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Public Health Service

National Toxicology Program Fiscal Year 1980 Annual Plan

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Toxicology Program FY 1980 Annual Plan

The National Toxicology Program Director announces the availability of the National Toxicology Program (NTP) Annual Plan for Fiscal Year 1980 and the bimonthly NTP Technical Bulletins; solicits comments on the Annual Plan; and urges all interested persons to propose chemical(s) for testing by NTP.

Background

The National Toxicology Program develops scientific information about potentially toxic and hazardous chemicals which can be used for protecting the health of the American people and for the primary prevention of chemically-induced disease. The National Toxicology Program centralizes and strengthens the DHEW's activities in toxicology research, testing, and test development/validation efforts and provides the necessary toxicological information needed by research and regulatory agencies. Three specific goals have been identified:

- To expand the toxicological profiles of the chemicals nominated, selected, and being tested;
- To increase the number and rate of chemicals under test;
- To develop, coordinate, and validate a series of test/protocols more appropriate for regulatory needs.

The National Toxicology Program's Charter Agencies—presently, the four DHEW agencies whose relevant toxicology programs comprise the NTP are the National Cancer Institute, National Institutes of Health; National Institute of Environmental Health Sciences, NIH; National Center for Toxicological Research; Food and Drug Administration; National Institute for Occupational Safety and Health, Center for Disease Control.

The NTP Executive Committee provides linkage between DHEW research and regulatory agencies to ensure that the toxicology research, testing, and test development carried out under the aegis of the NTP are responsive to the needs of those agencies and to the wants of the public. This unique and important aspect of the NTP brings together for the first time the research and regulatory agencies doing fundamental biomedical research. The governmental agencies that comprise the NTP Executive Committee are listed in the 1980 Annual Plan.

The NTP Board of Scientific Counselors provides scientific over-sight of the NTP. The NTP Board advises the NTP Director and the NTP Executive Committee on scientific content, philosophy, and policy and evaluates the merit and overall quality of the science conducted in the NTP components. Eight scientists (enumerated in the 1980 Annual Plan) have been appointed by the Secretary of the Department of Health, Education, and Welfare.

The program segments of the NTP are grouped into two categories—toxicologic research and testing, and coordinative management activities. Individual NTP scientists have been appointed as Leaders of the major program segments. Each scientist will be responsible for developing (in collaboration with other NTP colleagues) the subprogram activities, the implementation plan, as well as the coordination and supervision of the program work. Program and Project Leaders are listed in the 1980 Annual Plan.

The development and approval of the NTP Annual Plan remain central to the effective planning, coordination, and operation of the National Toxicology Program. As NTP Director, Dr. David P. Rall (also the Director of the National Institute of Environmental Health Sciences) reports to the Assistant Secretary for Health.

The National Toxicology Program's second annual plan consists of two parts separately bound: Part I, "NTP Annual Plan for Fiscal Year 1980" (NTP–79–7), describes current year research, testing, and validation efforts and resources. (Part I is printed in full following this announcement.) Part II, "NTP Review of Current DHEW Research Related to Toxicology" (NTP–79–8), lists chemicals being tested by DHEW agencies and describes toxicology methods currently being developed.

Written comments on the FY 1980 Annual Plan are welcome. These should be addressed to Dr. David P. Rall, Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, N.C. 27709, (telephone: (919) 541–3201 or FTS 629–3201).

An open meeting will be held in the Spring 1980 (date to be announced in the **Federal Register**) to receive suggestions for future directions of the NTP and to obtain comments on the FY 1980 Annual Plan.

Regarding chemical nomination, NTP urges all those interested in proposing chemical(s) for testing to do so, to recommend the type test(s) to be considered, and to supplement each nomination with the following *necessary* information, if known.

I. Chemical Identification.
a. Chemical Abstracts Service (CAS) preferred name
b. Common or Generic name and synonyms
c. CAS Registry Number
d. Chemical class and related compounds
e. Physical and chemical properties
  i. Physical description
  ii. Structural and molecular formula and molecular weight
  iii. Melting and boiling points
  iv. Solubility
  v. Stability and reactivity
  vi. Other relevant information
f. Commercial product(s) composition
g. References

II. Production, use, occurrence, and analysis
a. Production
  i. Source and synthesis, year and pathway of first production
  ii. Current production and pathway
b. Uses
c. Occurrence in the Environment
  i. Naturally occurring
  ii. Air, water, and soil
  iii. Occupational
d. Analysis
e. References

III. Toxicology
a. Human data, case reports, and epidemiological studies
b. Experimental animal information
c. *In vitro* and other short-term tests
d. Other relevant information
e. References

IV. Disposition and structure-activity-relations.
a. Absorption, distribution, metabolism, and excretion
b. Structure-activity correlations and considerations
c. References

V. Ongoing toxicological and environmental studies in the government, industry, and academia.

VI. Rationale for recommendation and suggested studies.

To bridge the yearly gap between Annual Plans, NTP has started a bimonthly NTP Technical Bulletin to keep those persons or groups interested in the NTP informed about the NTP's most current and proposed activities. The NTP Technical Bulletins augment the Annual Plans by more timely and frequent announcements of the NTP research activities and specific actions.

To receive the NTP Annual Plan for Fiscal Year 1980, the NTP Review of Current DHEW Research Related to Toxicology, or the NTP Technical Bulletin, please indicate which publications you wish to receive and return this information to: Ms. Leslie Gardner, NTP Publications, National Toxicology Program, P.O. Box 12233, Research Triangle Park, N.C. 27709.

Dated: January 31, 1980.

David P. Rall,

Director, National Toxicology Program.

National Toxicology Program; Annual Plan for Fiscal Year 1980

National Cancer Institute

National Institute of Environmental Health Sciences

National Center for Toxicological Research

National Institute for Occupational Safety and Health

[NTP-79-7; November 1979]

Department of Health, Education, and Welfare

National Toxicology Program

Annual Plan for Fiscal Year 1980

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Department of Health, Education, and Welfare, National Toxicology Program

Annual Plan for Fiscal Year 1980

Introduction and Executive Summary

The National Toxicology Program (NTP) aims to develop scientific information which can be used to protect the health of the American public from damage by exposure to environmental chemicals. Many human diseases can be traced to chemical exposure—lung cancer to asbestos, arsenic, bis(chloromethyl) ether and others; liver hemangiosarcoma to vinyl chloride; mesothelioma to asbestos; male sterility to kepone and dibromochlorpropane; neurologic disease to kepone, methyl mercury, lead and methyl butyl ketone. Preventing human exposure to such chemicals will prevent human disease.

The Department of Health, Education, and Welfare is responsible for safeguarding the public's health, and the prevention of human exposure to toxic chemicals remains a keystone in the Department's efforts to prevent disease and promote health.

Exposure to Chemicals

Lacking precise numbers, the extent of human exposure to chemicals can only be estimated—the number of chemicals, the intensity of exposures, and the number of people exposed being major components. Current estimates indicate that nearly 48,000 chemicals are used in commerce in the United States; for approximately 5000 of these production exceeds one million pounds/year, suggesting the possibility or potential for widespread and intense exposure. There are 5,500 food additives and 4,000 medicinal drugs. Further, humans are exposed to at least 1,200 additional compounds found in household products.

The universe of chemicals to which humans are exposed is therefore so large that the task of preventing human exposure to toxic chemicals might appear impossible.

Fortunately, most chemicals are relatively non-toxic and require few if any controls to protect human health. It appears that only a small fraction of these chemicals are highly toxic. Thus, to protect the public health and to prevent disease, this fraction should be accurately identified and rigidly controlled.

This then is a major task of the National Toxicology Program—to identify those toxic chemicals that must be controlled to prevent disease.

Carcinogenesis Lifetime Bioassay

What scientific tools do we have to do this? The standard tool is the two-sex, two-species lifetime study of experimental animals, usually rats and mice—beginning at weaning, ending at death, using multiple dose levels of the chemical being tested. Such a study can provide worthwhile information on the kinds of toxic effects caused by the chemical and the doses or concentrations causing these toxic effects. This standard test determines if a chemical causes cancer and produces damaging effects on certain organ systems—liver, lung, kidney, endocrine systems, etc. This test is weak at predicting effects on reproductive capacity, pre- and postnatal growth and development, certain enuro-behavioral functions, and at identifying chemicals that damage genetic information transfer—mutagens. Further, the study of even a single compound is expensive, costing hundreds of thousands of dollars, taking up to four years to complete, and requiring hundreds of hours of scarce professional time.

It is unreasonable even to attempt to study all 48,000 chemicals in this way. Current known world capacity permits the initiation of perhaps 300 such chemical tests each year, and the results published this year are from the tests begun four or more years ago. This capacity—even if financial resources were not limiting—could be no more than doubled in the next 5–10 years. At this rate, it would take an additional 80 years to study all currently existing chemicals. Further, approximately 500 new chemicals are introduced into commerce each year, and this would result in an additional backlog of some 40,000 untested chemicals.

Implementation of the Toxic Substances Control Act will impact on the overall issue of testing, yet the final result remains the same—in the next 80 years the chemical testing backlog would be decreased only moderately.

Thus, we cannot perpetually rely on two-species lifetime studies to identify those chemicals which need strict control because:

(1) These tests have scientific limitations—they can miss certain critical toxic effects.

(2) They are time consuming and expensive.

Nonetheless, the long term testing of compounds which are currently untested or inadequately tested, and for which there is significant human exposure, will continue and if resources permit will continue at an increased rate. Additionally, each compound will be tested more thoroughly than in the past.

Newer Testing Methods

Therefore, the National Toxicology Program must develop and validate new test methods that will allow us to determine more quickly and less expensively the full toxicologic potential of a compound. To do this, NTP must use advances in basic knowledge of biological processes to design these new methods. NTP is in a unique position to do this because through its Executive Committee, NTP joins the basic research of HEW to the more immediate needs of the regulatory agencies. The task is difficult, but it is of the highest importance and should result in major improvement in public health. This 80 Annal Plan details the NTP approach to this problem.

A number of new test methods are being validated in Fiscal Year 80. These include the microbial mutagenesis assays, mammalian cell transformations, and immunology, and neurobehavioral test batteries. If the scientific community, the regulatory agencies, and ultimately the public are to accept the test methods which are used by NTP and the private sector to determine if compounds pose toxicologic risks, then this validation process must include several assurances. Firstly, each test must be reproducible over time and among laboratories. Secondly, the test must measure or predict what it is expected to measure or predict. Thus, for example, a test must show that mutagenic compounds are mutagenic and that non-mutagenic compounds are not mutagenic.

Chemical Selection

The selection of compounds for the NTP testing process is critical. Input into the selection process comes mainly from the research and regulatory agencies on the Executive Committee, and will be specifically invited from other public and private sectors in FY 1980. In addition, a "Testing Needs Study" will be initiated. This study will show how many compounds should be tested for toxicity, indicate specific compounds which should be considered for testing and whether this process will provide useful input for the NTP chemical selection process.

NTP Annual Plan—FY 1980

This FY 80 Annual Plan consists of two major sections:

Part I: Research, Resources, and Program activities for FY 1980, and

Part II: Current DHEW research relating to toxicology (Parts I and II are bound as separate volumes).

The NTP program is described in Part I; however, important features of this FY 80 Annual Plan are highlighted:

Development of sequential test phases to allow identification of toxic chemicals are rapidly and precisely as possible. This will include short-term tests for mutagenesis, carcinogenesis, neurobehavioral toxicity, and general toxicity. Many of these tests have been developed and need either refinement and validation or only validation.

As resources permit, development of test systems to identify certain other toxic effects in laboratory animals—effects on the immune system, the cardiovascular system, certain aspects of the reproductive system, etc.

Prediction of the relation between level of exposure and extent of damage to human health. Termed quantitative risk assessment, this difficult process will assist regulatory agencies in protecting the public health at a minimal cost to the Nation's economy. NTP scientists are among the leaders in research in this area and will continue their efforts. Further, through the use of research grants, the strengths of the academic community will be brought to bear on this problem.

Maintenance of or, as resources permit, increases in the number of compounds being started on long (and short) term tests.

Development of a system for outside review of test results and validated test methods and a system for communicating these results as rapidly and as accurately as possible.

Development of a list of known and suspected carcinogens with the required supporting information such as estimates and nature of exposures; presence or absence of effluent, ambient, or exposure standards; and effectiveness of these standards. This information will be reported annually on a calendar year basis as required by Public Law 95-622.* Both DHEW agencies and the participating non-DHEW regulatory agencies are contributing to the development of this list.

Initiation of a program to determine the number of chemicals with the potential for significant human exposure and the fraction of those that have been adequately tested for toxic effects. This testing needs study will provide an assessment of how great is the problem of untested potentially toxic compounds.

Continuation of responsiveness to current health problems.

Specifically:

NTP is testing or has tested many chemicals found in toxic chemical waste dumps, such as the Love Canal.

NTP will initiate a program to test combinations of these chemicals.

NTP will continue to test components of Agent Orange.

NTP is studying the effects of oral ingestion of asbestos as well as the effects of the inhalation of fiberglass and various sizes of asbestos.

NTP will study selected toxic effluents from synfuel production that may create environmental and occupational hazards.

Background

On November 15, 1978, the Secretary of DHEW announced the establishment of the National Toxicology Program (NTP). The broad goal of the NTP is to strengthen the Department's activities in testing chemicals of public health concern, as well as to develop and validate new and better integrated test methods. The three specific goals for the Program are:

To broaden toxicological characterization of the chemicals being tested.

To increase the rate of chemical testing.

To develop and begin to validate a series of protocols more appropriate for regulatory needs.

To accomplish these goals the program was established as a Department-wide effort to provide needed information to regulatory and research agencies and to strengthen the science base. This Program is coordinated under the direction of Dr. David P. Rall, also the Director of the National Institute of Environmental Health Sciences, who for the purpose of this Program reports to the Assistant Secretary for Health.

*The Community Mental Health Centers Act, Amendments, Pub. L. 95-622, Title II, Part E. Section 262.

Central to the effective planning, coordination and operation of the National Toxicology Program is the development and approval of the Annual Plan.

Participating Agencies

Resources for the National toxicology Program in FY 79 came from the budgets of the participating DHEW agencies:

Food and Drug Administration, National Cancer Institute, National Institute for Occupational Safety and Health, and the National Institute of Environmental Health Sciences.

The segments of their operations committed to the National Toxicology Program totaled $41 million in FY 79. The estimated level of resource commitment in FY 80 approximates $69 million, but this has not been established since most DHEW appropriations have not been enacted or apportioned. The actual FY 79 agency dollar levels for NTP, and projected dollar levels for FY 80 are shown in Figure 1.

Other governmental agencies with a health oriented mission are invited to become participating members of the NTP and they should commit their toxicology related resources to the Program.

The capabilities of the NTP are also augmented through an interagency agreement with the National Library of Medicine that commits to the NTP certain toxicology-related portions of its technical information services.

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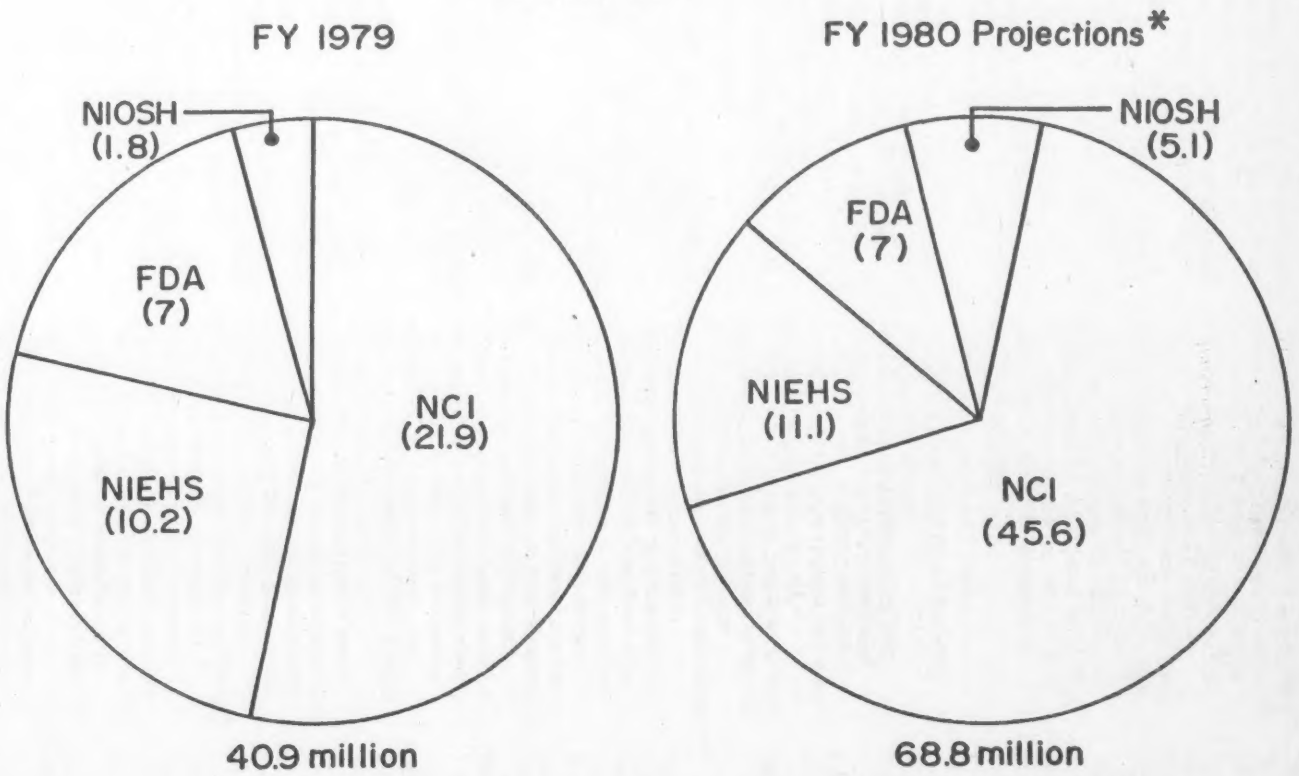
FIGURE 1

Agency origin and amounts of funding for NTP (millions)



* Based on House and Senate Labor - HEW Appropriations Committees Conferee Report. These monies have not been appropriated or apportioned.

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Oversight and Review

NTP Executive Committee

Key to the National Toxicology Program is the primary advisory group—the NTP Executive Committee. The Committee is composed of Heads of the Food and Drug Administration, Occupational Safety and Health Administration, Consumer Product Safety Commission, Environmental Protection Agency, National Institutes of Health, National Institute for Occupational Safety and Health, National Cancer Institute, and the National Institute of Environmental Health Sciences. Newly elected each year, the current Chairperson of the Executive Committee is Dr. Eula Bingham, Assistant Secretary for Occupational Safety and Health, Department of Labor. Active participation of Committee members at regular meetings assures continuing input from the research and regulatory agencies in the critical phases of operation: e.g., development and approval of chemical selection principles, a chemical nomination and selection process, protocol design and approval policy; selection and priority setting for chemicals to be placed on test; and input into program planning and balance. Committee members will continue their oversight in FY 80 by actively monitoring and evaluating the progress of the Program and advising on future directions, research, and testing needs. This unique and important aspect of NTP brings together for the first time the agencies performing fundamental biomedical research and the regulatory agencies who need these results.

NTP Board of Scientific Counselors

The National Toxicology Program's Board of Scientific Counselors will provide scientific oversight of the NTP. The Board will advise the Program Director and the Executive Committee on matters of scientific content and policy, and evaluate the merit and overall quality of the science conducted in the Program components. The Charter of the Board has been written and approved by the Executive Committee and the following eight scientists have been appointed by the Secretary, DHEW:

Joseph C. Dunbar, Ph.D., Wayne State University School of Medicine.

Curtis Harper, Ph.D., University of North Carolina School of Medicine.

Margaret Hitchcock, Ph.D., Yale University Medical School.

Marjorie G. Horning, Ph.D., Baylor College of Medicine.

Mortimer L. Mendelsohn, M.D., Ph.D., Lawrence Livermore Laboratory, University of California.

Norton Nelson, Ph.D., (*Chairperson*) New York University School of Medicine.

Thomas H. Shepard, M.D., University of Washington School of Medicine.

Alice S. Whittemore, Ph.D., Stanford University.

Public Comments

The needs for chemical testing and for test development and validation are greater than the resources available to NTP. To insure that the efforts of the NTP remain relevant to society, NTP actively solicits and encourages comments from everyone—scientists, public and private organizations, and individuals. Partly, this is accomplished by wide distribution of the Annual Plan (published in the **Federal Register**) and announcement of open meetings, held expressly to receive comments on current and future Annual Plans and to encourage nominations of chemicals for testing. The first open meeting, on the FY 79 Plan, was held August 10, 1979, in Washington, D.C., and many useful comments have been received.

An NTP open meeting will be scheduled for early spring to invite comments about this Annual Plan and to receive suggestions for future NTP activities.

Planning Assumptions and Program Balance

The FY 1979 operating level for the NTP was $41 million. The FY 1980 budget permits the continuation of NTP at the FY 1979 level. As Congressional action on the FY 1980 budget has not yet been completed, this NTP Annual Plan for FY 1980 is predicated on a continuation of the FY 1979 level of operation. If additional funds are made available in FY 1980, then an increase in the number of chemicals placed on test will be possible. In either event, the NTP activities for FY 1980 represent a balanced approach to fulfilling the specific goals established for the NTP:

To broaden toxicological characterization of chemicals being tested.

To increase the rate of chemical testing.

To develop and validate testing protocols more appropriate for regulatory needs.

In any fiscal year the final balance of the Program efforts that address the stated goals of the NTP is developed only after considering:

Available resources;

Testing mandates;

Solicitation of specific research and testing requirements from the regulatory agencies, health research agencies, and the public;

Guidance from the Board of Scientific Counselors as to what is feasible given the current science base, and

Endorsement of each Annual Plan by the Executive Committee.

There is Executive Committee consensus that the current Plan must address all three Program goals; therefore the initiatives in any one goal are limited by other competing program goals.

Implementation of the Toxic Substances Control Act (TSCA) should result in a gradual shift of many of the responsibilities for testing individual chemicals from the National Toxicology Program to the private sector. As that transfer occurs those activities that focus on the development, refinement, and validation of toxicologic test methodologies will be increased. Selection of chemicals will then focus on materials that reside outside TSCA requirements or related legislation (see page 79 for the Chemical Selection Principles adopted by the Executive Committee).

Organization

The scientific capabilities and resources of the participating agencies cover a broad range of toxicologic techniques and methods. All four agencies, for instance, conduct lifetime toxicity-carcinogenicity studies and some mutagenicity testing or test development. Three agencies are involved in neurobehavioral testing; two agencies study pulmonary toxicity, etc. Integration of these activities, begun in FY 79, will be more fully implemented in FY 80. Individual NTP scientists have been identified as leaders of major program segments. Each individual will serve as the center or contact for a particular program activity, and will be responsible for developing, in collaboration with appropriate NTP colleagues, the program objectives, the plan for implementing the program, as well as the coordination and supervision of the program's work. The programs and leaders are listed in Table 1.

The program segments of the National Toxicology Program are grouped into two categories: toxicologic research and testing, and coordinative management activities.

The toxicologic research and testing activities are responsible for development and supervision of contracts that extend these activities or perform indepth toxicologic chemical characterization. These activities include:

—Genetic toxicology
—Carcinogenesis
—Chemical disposition
—General toxicology
—Immunologic toxicology
—Neurobehavioral toxicology

Table 1.—*Major National Toxicology Program Areas and Leaders*

Area	Leader	Contributing agency [1]	Telephone No.
Director	Dr. D. P. Rall	NTP	(919) 541-3201
Deputy Director	Dr. J. A. Moore	NTP	(919) 541-3267
TOXCOLOGIC RESEARCH AND TESTING			
Carcinogenesis	Dr. R. Griesemer	NCI	(202) 496-5591
Short-Term Test Development	Vacant		
Tumor Pathology	Dr. J. Ward	NCI	(202) 496-6868
Chemical Disposition	Dr. H. Matthews	NIEHS	(919) 541-3369
General Toxicology	Dr. J. Moore	NTP	(919) 541-3267
Toxicopathology	Dr. E. McConnell	NIEHS	(919) 541-3231
Genetic Toxicology	Dr. E. Zeiger	NIEHS	(919) 541-4482
Immunologic Toxicology	Dr. J. Dean	NIEHS	(919) 541-4659
Neurobehavioral Toxicology	Dr. C. Mitchell	NIEHS	(919) 541-3220
Pulmonary Toxicology	Dr. T. Lewis	NIOSH	(513) 684-8392
Reproductive and Developmental Toxicology	Dr. J. Holson	NCTR	(501) 542-4303
COORDINATIVE MANAGEMENT ACTIVITIES			
Bioassay Coordination	Dr. J. F. Douglas	NCI	(202) 496-5591
Chemical Nomination	Dr. L. Fishbein	NCTR	(501) 542-4390
Chemical Repository	Dr. C. Jameson	NCI	(202) 496-1152
	Dr. D. Walters	NIEHS	(919) 541-3355
Data Management and Analysis	Dr. D. Hoel	NIEHS	(919) 541-3205
Carcinogenesis	Dr. K. Chu	NCI	(202) 496-1152
Mutagenesis	Dr. B. Margolin	NIEHS	(919) 541-3460
Toxicology	Dr. J. Haseman	NIEHS	(919) 541-3437
TDMS (Development)	MR. A. Konvicka	NCTR	(501) 542-4534
Information Dissemination	Dr. J. E. Huff	NTP	(919) 541-3780
Laboratory Animal Quality Control	Vacant		
Laboratory Health and Safety	Dr. H. Mahar	NCI	(202) 496-9526
Technical Information	Dr. H. Kissman	NLM	(202) 496-3147

[1] Addresses: National Cancer Institute, Bethesda, MD 20205; National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709; National Library of Medicine, Bethesda, MD 20014; National Toxicology Program, Research Triangle Park, NC 27709; National Institute for Occupational Safety and Health, Cincinnati, OH 45226; National Center for Toxicological Research, Jefferson, AR 72079.

[2] Dr. J. Haseman, Acting Program Leader.

—Data management and analysis
—Information dissemination
—Laboratory animal quality control
—Laboratory health and safety
—Technical information

Funding levels in FY 79 for both toxicologic research and testing, and coordinative management activities are shown in Figure 2.

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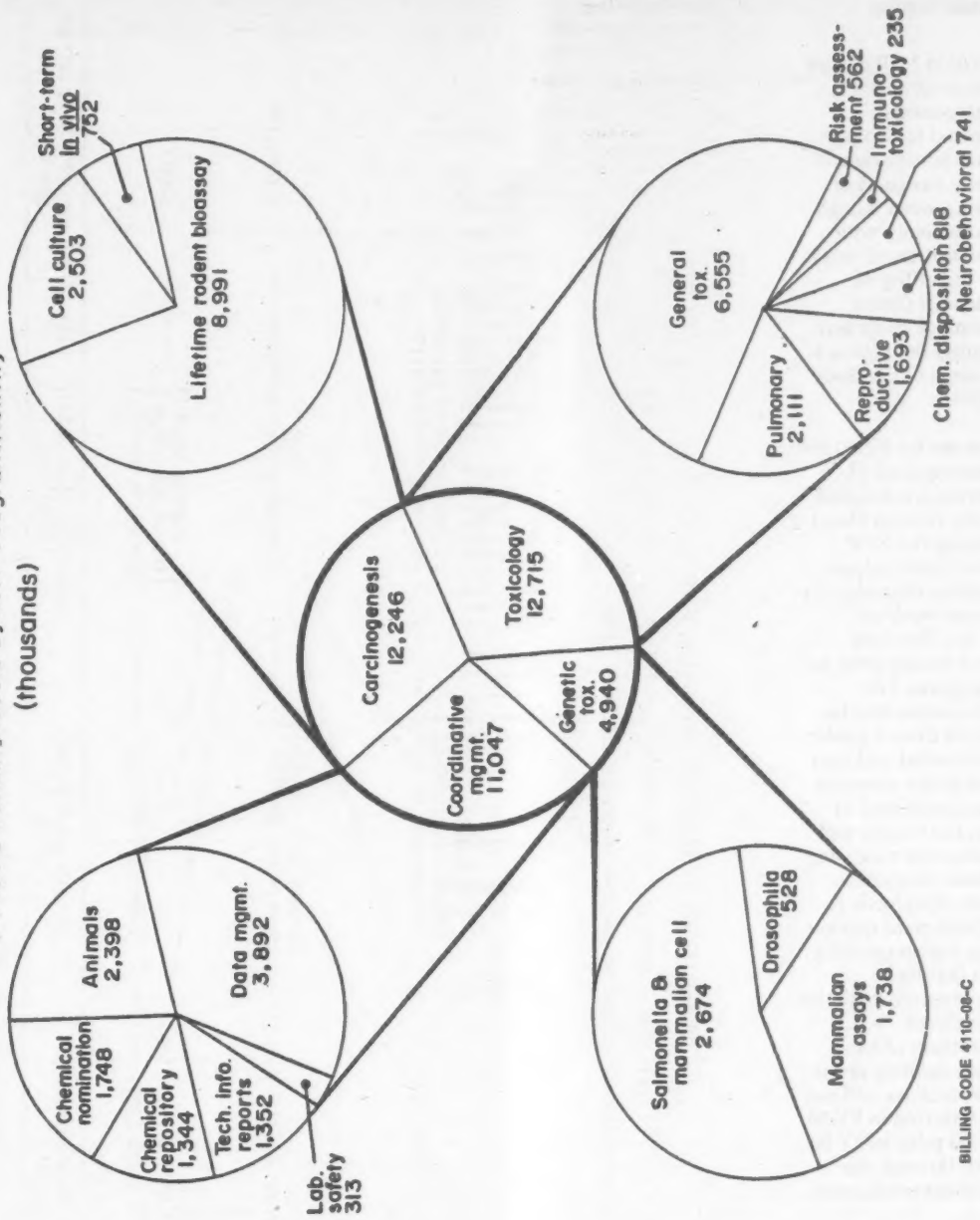
—Pulmonary toxicology
—Reproductive and developmental toxicology

The coordinative management activities are overarching in nature, and include:

—Bioassay coordination
—Chemical nomination and selection
—Chemical management
—Chemical repository

Figure 2

FY 1979 Funding levels by NTP Program Activity
(thousands)



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Toxicology Research and Testing Overview

Toxicology testing within NTP can be placed into three major programs: genetic toxicology (mutagenesis), carcinogenesis and general toxicology. For descriptive purposes some areas of toxicology are arbitrarily assigned to one of the three programs, even though these areas interact extensively with other programs. An illustration of cross program interaction is the utility of *Salmonella* mutation assays (listed within the genetic toxicology program) to the carcinogenesis program. Figure 3 depicts the major segments of the three testing programs and these interrelationships.

The major test initiatives for FY 80 are summarized below: (descriptions of specific program activities are detailed starting on page 23 in the Annual Plan.)

In carcinogenesis testing the NTP proposes to start 75 new chemicals on the lifetime carcinogenicity bioassays in FY 80. This is the same as the level achieved in FY 79 and is a two-fold increase over the rate of testing prior to establishment of the Program. The Program's strategy is to assure that the most important chemicals from a public health point of view are tested and that end results are relevant to the research and regulatory agencies interested in each chemical. Further, the results will provide better information for assessing risk associated with those chemicals found to be carcinogenic. Emphasis is also being given to validation of quicker methods of determining carcinogenicity.

The NTP determined that its carcinogenicity testing program could be best performed through direct management and supervision of each chemical test. Therefore, existing prime contract management resources will not be utilized for any tests started in FY 80; testing activities initiated prior to FY 80 will continue to proceed through the prime contract management mechanism.

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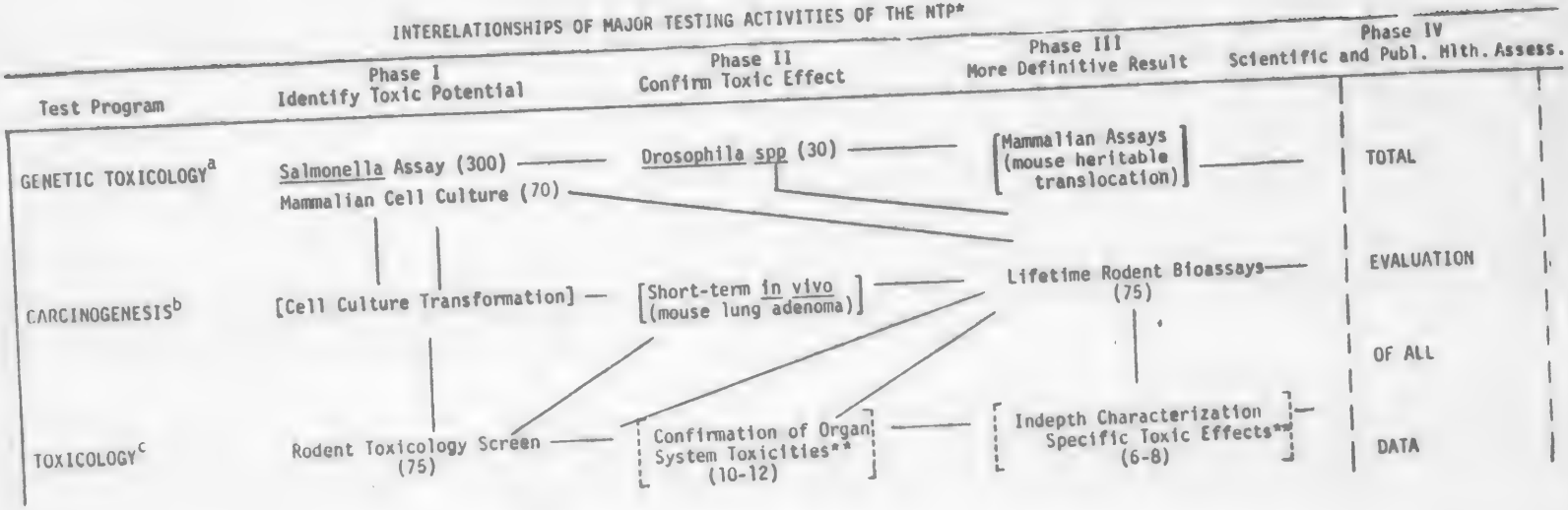
FIGURE 3

INTERELATIONSHIPS OF MAJOR TESTING ACTIVITIES OF THE NTP*



Key: * Based on the assumption of resources to include 75 lifetime rodent bioassays in FY 80

[ ] Some in validation phase

[ ] Test validation only

(#) Yearly capacity, FY 80 figures

** Capability varies according to specific organ

[a] See text, pp. 23-39

[b] See text, pp. 39-65

[c] See text, pp. 65-74

BILLING CODE 4110-08-C

Most chemicals selected for testing by NTP are selected because too little is known about their toxicologic effects and the potential exists for considerable human exposure. The NTP toxicology testing strategy, to be initiated in FY 80, is to identify with assurance the major toxic effects for each chemical studied on chronic tests (Figure 3). This will include damage to critical targets such as the lungs, liver, and nervous system, as well as the identification of carcinogens and mutagens. Thus, the Phase I tests should result in a core of toxicology data essential to the proper design of more extensive studies. Using the information from the Phase I rodent toxicologic screen, more extensive toxicologic testing can bae started with increased capabilities to confirm and define those toxicities identified in the screen. The plan in FY 80 is to initiate testing on 75 chemicals in the toxicologic screen and to enhance the toxicologic characterization capabilities in neurobehavioral toxicology, immunology, and chemical disposition. Fertility and reproductive toxicology, and cardiovascular toxicology continue to be inadequately addressed within NTP, and new test systems need to be developed and are being pursued.

A continuing area of major testing emphasis is genetic toxicology. NTP strategy for FY 80 is to increase the rate of *in vitro* microbial mutagenesis testing to 300 chemicals, to commence parallel testing in cultured mammalian cells at a rate of 70 chemicals, and to commence Phase II testing utilizing *Drosophila* systems at a rate of 30 chemicals per year. All chemicals selected for lifetime carcinogenicity bioassay and testing in the toxicologic screen will be first tested in the *in vitro* genetic toxicity tests.

The strategy for test development or validation is to review existing and emerging newer methodologies to determine which may be adequately sensitive and reporducible. Those most likely to offer improvements over older methods will be selected and validated. When basic research findings suggest new areas of toxicology testing, NIP will undertake the appropriate methods development and validation. Examples of existing methodology that are being examined for modification are techniques used to detect impaired liver or kidney function and neurobehavioral toxicity; new areas of methods development and validation include behavioral teratology, immunotoxicology, and short-term tests for presumptive carcinogenic potential.

Validation of test methods is a two stage process. First, does the procedure yield test results that are reproducible within and between laboratories? Second, does the test predict for toxic potential in humans? The latter requires that NTP pay close attention to the results of human epidemiological studies that may correlate with test results.

The NTP approach to testing will be directed to developing new or better test methods. This is not an indication of flaws in traditional toxicology or regulatory test requirements but reflects an area of science with rapidly expanding boundaries of knowledge. Thus, it is necessary that NTP have a planned strategy to validate possible alternatives that may be more reliably performed, yield new toxicologic data, yield results relevant to human disease, or develop a testing approach that produces equivalent results in a faster or more economical manner, NTP knows that its testing results often impact on regulatory or public health issues and NTP will constantly attempt to meld its innovative approaches with "standard" methods in a manner that ensures results that are germane and of utility to regulatory and public health needs. To the extent that NTP testing uses standard methods, NTP will attempt to incorporate those standards presently used by the regulatory agencies, such as the lifetime rodent bioassay. The tests used must be of the same quality as those required and used by laboratories in the private sector, e.g., in the chemical industry.

Genetic Toxicology

Mutagaenicity assays identify structural or functional DNA perturbations in germinal or somatic cells. Effects in germ cells are important for predicting potential undesirable effects of fertility, the developing conceptus, or in generations subsequent to that which received chemical exposure. Somatic mutation may be predictive for physiologic alterations in the exposed person and for the potential induction of cancer.

The strategy for testing is to develop a screening program consisting of three phases or tiers of testing that progress in complexity from simple systems composed of microbial or mammalian cells in culture to *Drosophila* systems and, finally, to specific whole animal mammalian systems. The mutagenicity test program and its interactions with other NTP programs is diagremmed in Figure 3.

The Phase I *Salmonella* mutagenicity assay was established in FY 79. During FY 79, three contracts were awarded for testing and an initial list of 191 chemicals selected (Table 2). Testing on some of these chemicals began in FY 79 and will continue in FY 80 while testing of the rest will begin in FY 80. Since the test capacity for FY 80 is programmed for 300 chemicals, additional chemicals are being selected with a partial listing shown in Table 3. This assay uses *Salmonella typhimurium* tester strains TA 98, 100, 1535, and 1537 (with and without metabolic activation).

Tests with cultures mammalian cells are the second component of Phase I. These tests are included because, unlike bacterial tests, they reflect chromosome damage as well as gene mutation. Testing capability is being established in FY 79 with 70 chemicals scheduled for test in FY 80.

Chemicals that are mutagenic in these assays will progress to Phase II. A select number of negative chemicals will be committed to further testing, taking into account such factors as known biological activity of related compounds and level of human exposure.

The Phase II initiative involves the use of the fruit fly, *Drosophila spp*, that possesses inherent chemical metabolic activation capability and provides more precise information on the types of mutations induced, the time course of induction, and demonstrates heritability of the induced mutation. Both sex linked recessive lethal mutations and heritable translocations will be measured. Testing capability is being established in FY 79 and testing will begin in FY 80 at a rate of 30 chemicals per year.

Table 2—Chemicals Scheduled for Testing in FY 1980 Using Salmonella Mutagenicity Assays

Primary name	CAS No.**
Acetamide	60-35-5
Acetin	26446-35-5
Acetyl-o-toluidine	120-66-1
Acrolein	107-02-8
3-Amino-α,α,α-trifluorotoluene	98-16-8
o-Aminophenol	95-55-6
Amyl nitrite	463-04-7
Aniline	62-53-3
o-Anisidine	90-04-0
*p-Anisidine	104-94-9
Anthracene	120-12-7
1-Aziridine ethanol	1072-52-2
Azobenzene	103-33-3
Azodicarbonamide	123-77-3
Benzaldehyde	100-52-7
Benzofuran	271-89-6
p-Benzoquinone dioxime	105-11-3
Benzyl salicylate	118-58-1
*Biphenyl	92-52-4
2-Biphenylamine	90-41-5
4-Biphenylamine	92-67-1
*Bisphenol A	80-05-7
Boric acid	10043-35-3
Bromobenzene	108-86-1
Bromoform	75-25-2
n-Butyl-para-aminobenzoate	94-25-7
Cacodylic acid	75-60-5
*Carbon disulfide	75-15-0
*Catechol	120-80-9
Chloral hydrate	902-17-0
Chlorendic acid	115-28-6
4-Chloro-α,α,α-trifluorotoluene	98-56-6
4-Chloro-3,5-dinitro-α,α,α-trifluorotoluene	393-75-9
4-Chloro-3-nitro-α,α,α-trifluorotoluene	121-17-5
Chlorobenzene	108-90-7
m-Chloronitrobenzene	121-73-3
*4-Chloronitrobenzene	100-00-5
*2-Chloronitrobenzene	88-73-3
*m-Chlorophenol	108-43-0

Table 2—Chemicals Scheduled for Testing in FY 1980 Using Salmonella Mutagenicity Assays— Continued

Primary name	CAS No.**
*o-Chlorophenol	95-57-8
*p-Chlorophenol	106-48-9
Cinnamaldehyde	104-55-2
m-Cresol	108-39-4
o-Cresol	95-48-7
p-Cresol	106-44-5
Crotonaldehyde	123-73-9
Cyanuric acid	108-80-5
Cyclohexanol	108-93-0
Cyclohexanone	108-94-1
*Diacetone acrylamide	2873-97-4
4,4'-Diamino-2,2'-stilbenedisulfonic acid	81-11-8
*2,4-Diaminophenol hydrochloride	95-86-3
Dibenzofurna	132-64-9
Diborane	19287-45-7
2,3-Dibromo-1-propanol	96-13-9
Di-n-butylamine	111-92-2
*1,2-Dichlorobenzene	95-50-1
*1,3-Dichlorobenzene	541-73-1
*1,4-Dichlorobenzene	106-46-7
*1,1-Dichloroethylene (vinylidene chloride)	75-35-4
Dichloroisocyanuric acid, sodium salt	2893-78-9
2,3-Dichloronitrobenzene	3209-22-1
*3,4-Dichloronitrobenzene	99-54-7
2,4-Dichloronitrobenzene	611-06-3
*2,3-Dichlorophenol	576-24-9
2,4-Dichlorophenol	120-83-2
*2,5-Dichlorohenol	38048-58-7
*2,6-Dichlorohenol	87-65-0
*3,4-Dichlorohenol	95-77-2
*3,5-Dichlorohenol	591-35-5
Diethanolamine	111-42-2
7-Diethylamino-4-methylcoumarin	91-44-1
Diethyl carbonate	1609-47-8
Diethyldichlorosilane	1719-53-5
*Diethylene glycol dimethyl ether (diglyme)	111-96-6
Diethyl ethylphosphonate	78-38-6
*di(2-ethylhexyl) phthalate	117-81-7
5,7-Dihydroxy-4-methylcoumarin	2107-76-8
Diisobutylketone	91-16-7
3,3'-Dimethoxybenzidine 2HCl	20305-40-0
Dimethylamine	124-40-3
*Dimethyl cyanamide	1467-79-4
N,N-Dimethylformamide	68-12-2
2,4-Dimethylphenol	105-67-9
*N,N-Dimethylurea	1320-50-9
*2,4-Dinitrotoluene	121-14-2
2,4-Dinitrofluorobenzene	70-34-8
Dioctyladipate	123-79-5
1,3-Dioxane (meta)	505-22-6
1,4-Dioxane	123-91-1
Diphenyl oxide (Diphenyl ether)	101-84-8
Diphenylhydantoin (Phenytoin)	57-41-0
1,2-Epoxypropane	75-56-9
Ethyl bromide	74-96-4
Ethyl chloride	75-00-3
Ethylene glycol	107-21-1
*Ethylenediamine	107-15-3
Ethylene thiourea	96-45-7
*Eugenol	97-53-0
*Ferrocene	102-54-5
1-Fluoro-2,4-dinitrobenzene (FDNB)	70-34-8
2-Fluorobenzoyl chloride	393-52-2
Formaldehyde	50-00-0
Furfural	98-01-1
Gallic acid	149-91-7
Glutaraldehyde	111-30-8
Hematoxylin	517-28-2
Hexabromobenzene	87-82-1
Hexabromobiphenyl	36355-01-8
Hexachlorobenzene	118-74-1
Hexachlorocyclopentadiene	2385-85-5
*Hexachloroethane	67-72-1
Hexachlorophene	70-30-4
Hexachlorobutadiene	87-68-3
Hydrazine sulfate	10034-93-2
Hydrazinobenzene (Phenylhydrazine)	100-63-0
Hydroquinone	123-31-9
Hydroquinone dimethyl ether	150-78-7
Hydroquinone monomethyl ether	150-76-5
4-Hydroxyacetanilide	103-90-2
Lignin sulfonic acid sodium salt	8062-15-5
Lithium chloride	7447-41-8
Maleic anhydride	108-31-6
Melamine	108-78-1
Methacrylic acid	80-62-6
o-Methoxyphenol (Guaiacol)	90-05-1
Methylhydrazine	60-34-4
Methyl salicylate	119-36-8
*beta-Methylumbelliferone	90-33-5

Table 2—Chemicals Scheduled for Testing in FY 1980 Using Salmonella Mutagenicity Assays— Continued

Primary name	CAS No.**
*Morpholine	110-91-8
Nickelocene	1271-28-9
1-Nitronaphthalene	86-57-7
*p-Nitrophenol	100-02-7
*2-Nitropropane	79-46-9
2-Nitro-α,α,α-trifluorotoluene	384-22-5
*3-Nitro-α,α,α-trifluorotoluene	98-46-4
Oxalic acid	144-62-7
Pentachlorobenzene	608-93-5
*Pentachloronitrobenzene	82-68-8
*Pentachlorophenol	87-86-5
*Phenyl salicylate	118-55-8
Phthalic anhydride	85-44-9
*beta-Picoline	108-99-6
*Picric acid	88-89-1
Piperazine	110-85-0
Piperonal	120-57-0
Propylene dichloride (1,2-Dichloropropane)	78-87-5
*1,2-Propylene glycol	57-55-6
Pyridine	110-86-1
*Quinoline	91-22-5
p-Quinone (p-Benzoquinone)	106-51-4
*Resorcinol	108-46-3
*Rhodanine	141-84-4
*Ricinoleic acid, Sodium salt	8323-95-5
Semicarbazide hydrochloride	563-41-7
Sodium aluminosilicate	1344-00-9
Sodium dehydroacetate	4418-26-2
Sodium fluoride	7681-49-4
cis-Stilbene (cis-1,2-Diphenylethene)	645-49-8
trans-Stilbene	645-49-8
*Terephthalic acid	100-21-0
tert-Butyl Hydroperoxide	110-05-4
1,2,3,5-Tetrachlorobenzene	634-90-2
1,2,3,4-Tetrachlorobenzene	634-66-2
Tetrachloroethylene	127-18-4
1,2,3,4-Tetrachloronaphthalene	20020-02-4
2,3,4,5-Tetrachloronitrobenzene	29804-67-7
2,3,5,6-Tetrachloronitrobenzene	879-39-0
*Tetrachlorophthalic anhydride	117-08-8
Tetrakis(hydroxymethyl)phosphonium	124-64-1
Tetraethyllead	78-00-2
Tetranitromethane	509-14-8
*Thiocarbanilide	102-08-9
*Thioglycolic acid, Sodium salt	68-11-1
*Toluene	108-88-3
Tributoxyethyl phosphate	78-51-3
*Tributyl borate	688-74-4
*1,2,3-Trichlorobenzene	87-61-6
*1,2,4-Trichlorobenzene	120-82-1
*1,3,5-Trichlorobenzene	108-70-3
2,4,6-Trichlorophenol	88-06-2
*Triethanolamine	102-71-6
Trihydroxybutyrophenone	52262-23-4
*Triphenylphosphine	603-35-0
tris(2-Chloroethyl)phosphate	115-96-8
tris(2-Ethylhexyl)phosphate	78-42-2
*o-Tritolyl phosphate	78-30-8
p-Tritolyl phosphate	78-32-0
m-Xylene	108-38-3
o-Xylene	95-47-6
p-Xylene	106-42-3

*Testing Begun in FY 79.
**Chemical Abstract Service Registry Number.

Table 3.—*Chemicals Selected for Testing in FY 1980 Using Salmonella Mutagenicity Assays*

Primary name	CAS No.*
2,4'-Biphenyldiamine	492-17-1
bis(Chloroendo) furan	–
Bromocyclohexanol	22306-22-0
2-Butanone peroxide	1338-23-4
Chloral (Trichloroacetaldehyde)	75-87-6
2-Chloro-1,3-Butadiene	126-99-8
Copper acetoarsenite	12002-03-8
2,4-Dichlorophenoxyacetic acid (2,4-D)	94-75-7
Dichlorodiphenylethane (p,p'-DDE)	72-55-9
Dimethoxane	828-00-2
4,6-Dinitro-2-aminophenol	96-91-3
2-Ethylhexyl diphenyl phosphate	1241-94-7
Hexamethyl-p-rosaniline (gentian violet)	548-62-9
Maleic hydrazide	123-33-1
N-Methyl-p-aminophenol	150-75-4

Table 3.—*Chemicals Selected for Testing in FY 1980 Using Salmonella Mutagenicity Assays—* Continued

Primary name	CAS No.*
3-Methyl-3-phenylglycidic acid ethyl ester	77-83-8
Neophytadiene	504-96-1
N-Nitrosodiethanolamine	1116-54-7
Pentachloroanisole	1825-21-4
Pentachloronaphthalene	1321-64-8
Pentachlorophenyl methyl sulfide	1825-19-0
Phorbol ester	17673-25-5
1(2H)-Phthalazinone	119-39-1
Polybrominated biphenyls	–
Sodium dichloroisocyanurate	2893-78-9
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6
Tetramethyllead	75-74-1
Trichloronaphthalene	1321-65-9
2,4,5-trichlorophenoxy acetic acid (2,4,5-T)	93-76-5
tris(4-Bromophenyl)phosphate	–
tris(Isopropylphenyl)phosphate	–
Wollastonite calcium silicates	13983-17-0

*Chemical Abstract Service Registry Number.

The chemicals that are postive in the Phase II systems will be subjected to testing in whole animal systems, Phase III. The objective of these tests is to obtain information on the types of mutations produced *in vivo*, the heritability and germ cell sensitivity of the effect, the organs involved, and dose-response information. Chemicals producing germ cell damage or mutations will be further tested in animal systems to gather information for use in risk assessment.

The potential Phase III tests are in need of validation. The FY 80 plan is to commence validation efforts in several laboratories with the mouse heritable translocation assay.

In conjunction with the testing of chemicals for mutagenicity, the genetic toxicology initiatives also include test system validation and new test method development for all phases. NTP will identify not only which chemicals are mutagenic, but also which tests are most valid for determining mutagenicity. Finally, another important aim of the activity is to foster the integration of genetic endpoints with those of other long- and short-term toxicology tests. This would allow the same group of animals to be used to determine genetic effects as well as other toxicologic endpoints, thereby reducing the total expense of the tests.

Table 4.—Chemicals Being Tested in Salmonella/ Microsome Plate Assays For Comparison With Fischer 344 Rat and B.C.F. Mouse Lifetime Carcinogenesis Bioassays*

Chemical	CAS No.**
Acetohexamide	968-81-0
Acetylsalicyclic acid (Aspirin)	50-78-2
Aldicarb	116-06-3
2-Aminoanthraquinone	117-79-3
4-Amino-2-nitrophenol	119-34-6
2-Amino-5-nitrothiazole	121-66-4
Aniline hydrochloride	142-04-1
o-Anisidine hydrochloride	134-29-2
p-Anisidine hydrechloride	20265-97-8

Table 4.—Chemicals Being Tested In Salmonella/Microsome Plate Assays For Comparison With Fischer 344 Rat and $B_6C_3F_1$ Mouse Lifetime Carcinogenesis Bioassays*—Continued

Chemical	CAS No.**
APC (Acetylsalicylic Acid, Phenacetin, Caffeine)	8003-03-0
1,2,3-Benzotriazole	95-14-7
Caffeine	58-08-2
4'-Chloroacetyl(acetanilide)	140-49-8
p-Chloroaniline	106-47-8
3-Chloromethylpyridine hydrochloride	6959-48-4
4-Chloro-m-phenylenediamine	5131-60-2
Cinnamyl anthranilate	87-29-6
Coumaphos	56-72-4
m-Cresidine	102-50-1
p-Cresidine	120-71-8
Cupferron	135-20-6
2,4-Diaminoanisole sulfate	615-05-4
Diazinon	333-41-5
tris(2,3-Dibromopropyl)phosphate	126-72-7
1,3-Dichloro-5,5-dimethylhydantoin	118-52-5
N,N'-Dicyclohexylthiourea	1212-29-9
2,4-Dimethoxyaniline	54150-69-5
3,3'-Dimethoxybenzidine-4,4'-diisocyanate	91-93-0
4,4'-bis(Dimethylamino)benzophenone	90-94-8
2,4-Dinitrotoluene	121-14-2
Dyrene(anilazine)	101-05-3
Ethylenediaminetretraacetic acid, sodium salt	60-00-4
Ethylene dibromide	106-93-4
Fluometuron	2164-17-2
Lithocholic acid	434-13-9
dl-Menthol	89-78-1
4,4'-Methylenebis(N,N'-dimethylaniline)	101-61-1
3-Methyl-1-phenyl-2-pyrazolin-5-one	89-25-8
1,5-Naphthalenediamine	2243-62-1
Nitrilotriacetic acid trisodium salt monohydrate	18662-53-8
Nitrofen	1836-75-5
2-Nitro-p-phenylenediamine	5307-14-2
4-Nitro-o-phenylenediamine	99-56-9
3-Nitropropionic acid	504-88-1
5-Nitro-o-toluidine	99-55-8
Phenazopyridine hydrochloride	136-40-3
p-Phenylenediamine	106-50-3
Pivalolactone	1966-56-9
Proflavin hydrochloride	952-23-8
p-Quinone dioxime	105-11-3
Reserpine	50-55-5
Styrene	100-42-5
Succinic Acid, 2,3-dimethylhydrazine	1596-84-5
Sulfisoxazole	127-69-5
2,3,5,6-Tetrachloro-4-nitroanisole	2438-88-2
2,5-Toluenediamine sulfate	6369-59-1
Triphenyltin	76-87-9
1-Tryptophan	73-22-3

*Testing of all chemicals to be completed in FY 80.
**Chemical Abstract Service Registry Number.

A *Salmonella*/microsome plate assay has been standardized and found to yield reproducible results within and between several laboratories. This protocol uses *Salmonella typhimurium* strains TA 98, 100, 1535, 1537, and 1538, with and without metabolic activation. Liver S-9 preparations are prepared from both noninduced and Arochlor 1254 (polychlorinated biphenyls) induced $B_6C_3F_1$ mice, Fischer 344 rats, or Syrian hamsters. A series of 58 chemicals (Table 4) are being assayed which have been tested previously by lifetime carcinogenesis bioassays in $B_6C_3F_1$ mice and Fischer 344 rats, and for which stable lots of the original chemical are available. The purpose is to determine whether the same type of species variation observed in the animal bioassays will be detected in the mutagenicity assays. Each chemical will be tested under code in four laboratories which will assess further the interlaboratory reproducibility. These studies should be completed in FY 80.

Other assays being developed or validated include *Escherichia coli* WP2 uvrA, pol A+, and pol A− and the mammalian systems L5178Y mouse lymphoma [TK+/locus] and ARL6 rat liver.

NTP has assumed partial support of and participation in an international collaborative study with the objective of systematically evaluating a range of short-term assay systems for their ability to predict chemical carcinogenicity. The responses of approximately 30 assay systems are being analysed for 42 coded carcinogens and noncarcinogens. The chemicals tested and the assay systems used are listed in Tables 5 and 6. All assays have been completed in FY 79 with decoding and combined analysis scheduled for the first quarter of FY 80. The NTP will hold a public meeting on December 3, 1979, to present a preliminary assessment of results from the three-year study.

Table 5.—*International Program for the Evaluation of Short-Term Tests for Carcinogenicity; Compounds Tested*

Carcinogen/Noncarcinogen Pairs	
4-Nitroquinoline-n-oxide—56-57-5[1]	Chloroform—67-66-3.
3-Methyl-4-nitroquinoline-n-oxide-14073-00-8	1,1,1-Trichloroethane—71-55-6
Benzidine—92-87-5	2-Acetylaminofluorene—53-96-3
3,3', 5,5'-Tetramethylbenzidine—54827-17-7	4-Acetylaminofluorene—28322-02-3
4-Dimethylaminoazobenzene (Butter Yellow)—60-11-7	N-Nitrosomorpholine—59-89-2
4-Dimethylaminoazobenzene-4-sulphonic acid	Diphenylnitrosamine—86-30-6
Sodium salt (Methyl Orange)—547-58-0	Dinitrosopentamethylenetetramine—101-25-7
Urethane—51-79-6	1-Napthylamine—134-32-7
O-Isopropyl-N-3-chlorophenylcarbamate—101-21-3	2-Naphthylamine—91-59-8
Benzo(a)pyrene—50-32-8	Dimethyl carbamoyl chloride—79-44-7
Pyrene—129-00-0	Dimethylformamide—68-12-2
β-Propiolactone—57-57-8	Methylazoxymethanol acetate—592-62-1
α-Butyrolactone—96-48-0	Azoxybenzene—495-48-7
9,10-Dimethylathracene—781-43-1	dl-Ethionine—67-21-0
Anthracene—120-12-7	Methionine—63-68-3.

Table 5.—*International Program for the Evaluation of Short-Term Tests for Carcinogenicity; Compounds Tested* —Continued

Carcinogen/Noncarcinogen Pairs
Miscellaneous Compounds:
Hydrazine sulphate—10034-93-2.
Hexamethylphosphoramide (HMPA)—680-31-9
Ethylenethiourea—96-45-7
Diethylstilbestrol—56-53-1
Safrole—94-59-7
Cyclophosphamide—50-18-0
Epichlorohydrin—106-89-8
3-aminotriazole—61-82-5
4,4'-Methylenebis(2-chloroaniline)—101-14-4
Sugar (sucrose)—57-50-1
o-toluidine—95-53-4
Ascorbic acid—50-81-7
Auramine—492-80-8.

[1] Chemical Abstract Service Registry Number.

Table 6.—*International Program for the Evaluation of Short-Term Tests for Carcinogenicity—Assay Systems*

Prokaryotic Systems	
Repair deficiency assays	Point mutation assays
Bacillus subtilis-rec [-]	Salmonella typhimurium/microsome (Ames test).
Escherichia coli-rec [-]	Salmonella typhimurium 8-azaguanine resistance.
Escherichia coli-pol A [-]	Escherichia coli WP-2.
Phage Induction	Escherichia coli 343/113.

Eukaryotic Systems

Fungus:
- Saccharomyces cerevisiae—mitotic recombination.
- Saccharomyces cerevisiae—reversions.
- Schizosaccharomyces pombe—forward mutations.
- Saccharomyces cerevisiae.

Plant:
- Tradescantia—stamen hair system.

Insect:
- Drosophila melanogaster—sex-linked recessive lethals.

Mammal (in vitro):
- Unscheduled DNA Synthesis (human cells).
- Sister chromatid exchange (CHO cells).
- Chromosome aberrations (hamster and rat cells).
- Specific Locus mutations.
  - L5178Y cells—TK and HGPRT
  - P388F cells-TK and HGPRT.
  - CHO cells-HGPRT.
  - Human fibroblasts-HGPRT.
  - Human fibroblasts-Diptheria toxin resistance.

Mammal (in vivo):
- Micronucleus (mouse).
- Chromosome aberrations.
- Sister-chromatid exchange (mouse, rabbit).
- Sperm morphology (mouse).

Nongenetic Systems

- *In vitro* Nuclear Enlargement.
- Rabbit Test
- Transformation (BHK Cells).

Table 7.—*Chemicals Being Tested in Fiscal Year 1979 Using Carcinogenesis Bioassays*

Chemical	CAS No.[1]	Route	Species
Acid black 52	5610-64-0	Feed intratr	Rat/hamster.
Acid orange #3	6373-74-6	Feed	Rat/mouse.
Agar agar	9002-18-0	Feed	Rat/mouse.
Agaritine	2757-90-6	Water	Rat/mouse.
Allyl isothiocyanate	57-06-7	Gavage	Rat/mouse.
Allyl isovalerate	2835-39-4	Gavage	Rat/mouse.
2-Amino-4-nitrophenol	99-57-0	Feed	Rat/mouse.
2-Amino-5-nitrophenol	121-88-0	Feed	Rat/mouse.
Aminoundecanoic acid	27323-47-3	Feed	Rat/mouse.
Ampicillin trihydrate	69-53-4	Feed	Rat/mouse.
Antimony oxide	1309-64-4	Feed	Rat/mouse.
Asbestos, amosite	12172-73-5	Feed	Rat/hamster.
Asbestos, chrysotile SR	12001-29-5	Feed	Rat/hamster.
Asbestos, chrysotile IR	12001-29-5	Feed	Rat/hamster.
Asbestos, chrysotile SR	12001-29-5	Inhal	Rat.
Asbestos, chrysotile IR	12001-29-5	Inhal	Rat.
Asbestos, crocidolite	12001-28-4	Feed	Rat.
Ascorbic acid	50-81-7	Feed	Rat/mouse.
Benzene	71-43-3	Gavage	Rat/mouse.
Benzofuran	271-89-6	Gavage	Rat/mouse.
Benzoin	11953-9	Feed	Rat/mouse.
Benzyl acetate	140-11-4	Gavage	Rat/mouse.
Benzyl alcohol	100-51-6	Gavage	Rat/mouse.
Benzyl chloride	100-44-7	Gavage	Mouse.
2-Biphenylamine hydrochloride	90-41-5	Feed	Rat/mouse.

Table 7.—*Chemicals Being Tested in Fiscal Year 1979 Using Carcinogenesis Bioassays—Continued*

Chemical	CAS No.[1]	Route	Species
2,2-Bis(bromomethyl)-1,3-propanediol	3296-90-0	Gavage	Rat/mouse.
Bis(2-chloro-1-methylethyl) ether	108-60-1	Gavage	Rat/mouse.
Bisphenol A	80-05-7	Feed	Rat/mouse.
HC blue 1	2784-94-3	Feed	Rat/mouse.
Blue 15B	574-93-6	Feed	Rat/mouse.
Boric acid	10043-35-3	Feed	Mouse.
Bromobenzene	108-86-1	Gavage	Rat/mouse.
Bromoform	75-25-2	Gavage	Rat/mouse.
Bromodichloromethane	75-27-4	Gavage	Rat/mouse.
1,3-Butadiene	106-99-0	Inhal	Mouse.
2-Butanone peroxide (MEK peroxide)	1338-23-4	SP	Rat/mouse.
Butyl benzyl phthalate	85-68-7	Feed	Rat/mouse.
n-Butyl chloride	109-69-3	Gavage	Rat/mouse.
t-Butyl alcohol	75-65-0	Water	Rat/mouse.
Caprolactam	105-60-2	Feed	Rat/mouse.
Castor oil	8001-79-4	Feed	Rat/mouse.
Chlorendic acid	115-28-6	Feed	Rat/mouse.
Chlorinated trisodium phosphate	56802-99-4	Gavage	Rat/mouse.
Chlorobenzene	108-90-7	Gavage	Rat/mouse.
Chlorodibromomethane	124-48-1	Gavage	Rat/mouse.
3-Chloro-2-methylpropene	563-47-3	Gavage	Rat/mouse.
Chlorowax 40	51990-12-6	Gavage	Rat/mouse.
Chlorowax 500C	56509-64-9	Gavage	Rat/mouse.
Chlorpheniramine maleate	113-92-8	Gavage	Rat/mouse.
Cinnamyl anthranilate	87-29-6	Feed	Rat/mouse.
Coconut oil acid diethanolamine (con 2/1)	8040-31-1	SP	Rat/mouse.
Cyclohexanone	108-94-1	Water	Rat/mouse.
Cytembena	2126-70-7	IP/INJ	Rat/mouse.
D & C red no. 9	5160-02-1	Feed	Rat/mouse.
Decabromodiphenyl oxide	1163-19-5	Feed	Rat/mouse.
Diallylphthalate	131-17-9	Gavage	Rat/mouse.
1,4-Diamino-2,6-dichlorobenzene	609-20-1	Feed	Rat/mouse.
Dibromochloropropane (DBCP)	96-12-8	Inhal	Rat/mouse.
1,2-dibromethane	106-93-4	Inhal	Rat/mouse.
2,3-Dibromo-1-propanol	96-13-9	Gavage	Rat/mouse.
o-Dichlorobenzene	95-50-1	Gavage	Rat/mouse.
p-Dichlorobenzene	106-46-7	Gavage	Rat/mouse.
1,2-Dichloroethylene	540-59-0	Gavage	Rat/mouse.
2,4-Dichlorophenol	120-83-2	Feed	Rat/mouse.
1,2-Dichloropropane	78-87-5	Gavage	Rat/mouse.
1,3-Dichloropropene	542-75-6	Gavage	Rat/mouse.
Diesel fuel marine	.....	Gavage	Rat.
		SP	Mouse.
Diethanolamine	111-42-2	Water	Rat/mouse.
Di(2-ethylhexyl)adipate	103-23-1	Feed	Rat/mouse.
Di(2-ethylhexyl)phthalate	117-81-7	Feed	Rat/mouse.
Diglycidylresorcinol ether	101-90-6	Feed	Rat/mouse.
N,N-Dimethylaniline	121-69-7	Gavage	Rat/mouse.
N,N-Dimethyldodecylamine oxide	1643-20-5	Water	Rat/mouse.
Dimethyl hydrogenphosphite	868-85-9	Gavage	Rat/mouse.
Dimethyl methylphosphonate	756-79-6	Gavage	Rat/mouse.
Dimethyl morpholinophosphoramidate	597-25-1	Gavage	Rat/mouse.
Dimethyl vinylchloride	513-37-1	Gavage	Rat/mouse.
Diphenhydramine hydrochloride	147-24-0	Feed	Rat/mouse.
4,4'-Diphenylmethane diisocyanate	101-68-8	Gavage	Rat/mouse.
Disperse blue #1	2475-45-8	Feed	Rat/mouse.
Disperse yellow #3	2832-40-8	Feed, intratr	Rat/mouse.
Dodecyl alcohol, ethoxylated	9002-92-0	Feed	Rat/mouse.
Ephedrine sulphate	134-72-5	Feed	Rat/mouse.
1,2-Epoxyhexadecane	7320-37-8	SP	Rat/mouse.
Erythromycin stearate	643-22-1	Feed	Rat/mouse.
Ethyl acrylate	140-88-5	Gavage	Rat/mouse.
Ethylene chlorohydrin	107-07-3	SP	Rat/mouse.
Ethylene glycol monoethyl ether	110-80-5	Gavage	Rat/mouse.
Ethylene thiourea	96-45-7	Feed	Rat/mouse (pre- and post-natal).
Eugenol	97-53-0	Feed	Rat/mouse.
Fibrous glass	.....	Inhal	Rat.
Fluometuron	2164-17-2	Feed	Rat/mouse.
Fluorescein, disodium salt	518-47-8	Water	Rat/mouse.
Furosemide	54-31-9	Feed	Rat/mouse.
Geranyl acetate	105-87-3	Gavage	Rat/mouse.
Gibberellic acid	77-06-5	Feed	Rat/mouse.
Gilsonite	12002-43-6	SP	Rat/mouse.
Glutaraldehyde	111-30-8	SP	Rat/mouse.
Glycidol	556-52-5	Gavage	Rat/mouse.
Guar gum	9000-30-0	Feed	Rat/mouse.
Gum arabic	9000-01-5	Feed	Rat/mouse.
Gum tara	39300-88-4	Feed	Rat/mouse.
HC blue #2	33229-34-4	Feed	Rat/mouse.
HC red #3	2871-01-4	Feed	Rat/mouse.
Hematoxylin	517-28-2	SP/gav	Rat/mouse.
1,2,3,6,7,8,-Hexachlorodibenzo-p-dioxin (HCDD)	57653-85-7	Gavage	Rat/mouse.
		SP	Mouse.
Hexamethyl-p-rosaniline (gentian violet)	548-62-9	NCTR	
Hexylresorcinol	136-77-6	Feed	Rat/mouse.
Hydrochlorothiazide	36355-01-8	Feed	Rat/mouse.
Hydroquinone	123-31-9	SP/gav	Rat/mouse.
8-Hydroxyquinoline	148-24-3	Feed	Rat/mouse.
Iodinated glycerol	5634-39-9	Gavage	Rat/mouse.
Isophorone	78-59-1	Gavage	Rat/mouse.
Lauric acid diethanolamine (con 1/1)	120-40-1	SP	Rat/mouse.

Table 7.—*Chemicals Being Tested in Fiscal Year 1979 Using Carcinogenesis Bioassays—Continued*

Chemical	CAS No.[1]	Route	Species
d-Limonene	5989-27-5	Gavage	Rat/mouse.
Locust bean gum	9000-40-2	Feed	Rat/mouse.
Malathion	121-75-5	Feed	Rat.
Maleic hydrazide diethanolamine salt	5716-15-4	Water	Rat/mouse.
Malonaldehyde	542-78-9	Water	Rat/mouse.
Mannitol	[illegible]	Feed	Rat/mouse.
Melamine	108-78-1	Feed	Rat/mouse.
Methapyrilene	91-80-5	Feed	Rat/mouse.
8-Methoxypsoralen	298-81-7	Gavage	Rat/mouse.
alpha-Methylbenzyl alcohol	98-85-1	Gavage	Rat/mouse.
4,4'-Methylenebis(N,N'-dimethyl) aniline	101-61-1	Feed	Rat/mouse.
Methyl carbamate	598-55-0	Gavage	Rat/mouse.
Methyldopa	555-30-6	Feed	Rat/mouse.
Methylenedianiline	101-77-9	Feed	Rat/mouse.
Methylene chloride	75-09-2	Gavage	Rat/mouse.
		Inhal.	Rat/mouse.
Methyl methacrylate	[illegible]	Inhal.	Rat/mouse.
Mirex	2385-85-5	Feed	Rat.
Molybdate orange	12656-85-8	Feed	Rat/mouse.
Monuron	150-68-5	Feed	Rat/mouse.
Nalidixic acid	389-08-2	Feed	Rat/mouse.
Naphthalene	91-20-3	Gavage	Rat/mouse.
Navy fuels JP-5 (petroleum derived)		SP	Mouse.
		Garage	Rat.
Nitrofurantoin	67-20-9	Feed	Rat/mouse.
Nitrofurazone	59-87-0	Feed	Rat/mouse.
N-Nitrosodiethanolamine	1116-54-7	Water	Rat/mouse.
Oleic acid diethanolamine (con 1/1)	13961-86-9	SP	Rat/mouse.
Orange #10	1936-15-8	Feed	Rat/mouse.
Oxalic acid	144-62-7	Feed	Rat/mouse.
4,4'-Oxydianiline	101-80-4	Feed	Rat/mouse.
Oxytetracycline	79-57-2	Feed	Rat/mouse.
Penicillin VK	132-98-9	Feed	Rat/mouse.
Pentachloroethane	76-01-7	Gavage	Rat/mouse.
Pentachlorophenol (dowicide EC-7)	(87-86-5)	Feed	Mouse.
Pentachlorophenol	[illegible]	Feed	Mouse.
Pentachlorophenol, technical	(87-86-5)	Feed	Mouse.
Phenol	108-95-2	Water	Rat/mouse.
Phenylbutazone	[illegible]	Water	Rat/mouse.
Phenolphthalein	77-09-8	Feed	Rat/mouse.
Phenylephrine hydrochloride	61-76-7	Feed	Rat/mouse.
N-Phenyl-2-naphthylamine	[illegible]	Feed	Rat/mouse.
o-Phenylphenol	90-43-7	SP	Mouse.
Phenytoin (diphenylhydantoin)	57-41-0	Feed	Rat/mouse (pre- and post-natal).
Phthalocyanine green	1328-53-6	Feed	Rat/mouse.
Polybrominated biphenyls		Feed	Rat/mouse (pre- and post-natal).
Propylene	115-07-1	Inhal.	Rat/mouse.
Propylene oxide	75-56-9	Inhal.	Rat/mouse.
Propyl gallate	121-79-9	Feed	Rat/mouse.
Pyridine	110-86-1	Gavage	Rat/mouse.
Red #14	3567-69-9	Feed	Rat/mouse.
Reserpine	50-55-5	Feed	Rat/mouse.
Rhodamine 6B	989-38-8	Feed	Rat/mouse.
p-Rosaniline hydrochloride	569-61-9	Feed	Rat/mouse.
Rotenone	83-79-4	Feed, NCTR	Rat/mouse.
Selenium sulfide	7488-56-4	Gavage	Rat/mouse.
		SP	Mouse.
Selsun (commercial)	UNK	SP	Mouse.
Sodium aluminosilicate	1344-00-9	Feed	Rat/mouse.
Sodium cyanurate	2624-17-1	Gavage	Rat/mouse.
		Water	Rat/mouse.
Sodium dodecyl sulfate	151-21-3	Feed	Rat/mouse.
Sodium(2-ethylhexyl)alcohol sulfate	126-92-1	Feed	Rat/mouse.
Sodium fluoride	7681-49-4	Water	Rat/mouse.
Stannous chloride	7772-99-8	Feed	Rat/mouse.
Styrene oxide	96-09-3	Gavage	Rat/mouse.
Succinic anhydride	108-30-5	Gavage	Rat/mouse.
Sudan 1	842-07-9	Feed	Rat/mouse.
Sulfamethazine	57-68-1	Gavage	Rat/mouse.
Sunset yellow FCF #6	2783-94-0	Feed	Rat/mouse.
Telone	542-75-6	Gavage	Rat/mouse.
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	1746-01-6	Gavage	Rat/mouse.
		SP	Mouse.
1,1,1,2-Tetrachlorethane	630-20-6	Gavage	Rat/mouse.
Tetrachloroethylene	127-18-4	Inhal.	Rat/mouse/hamster.
Tetranitromethane	509-14-8	Inhal.	Rat/mouse.
THPC	124-64-1	Feed	Rat/mouse.
THPS	UNK	Feed	Rat/mouse.
Toluene-2,6-diamine dihydrochloride	823-40-5	Feed	Rat/mouse.
Toluene diisocyanate	584-84-9	Gavage	Rat/mouse.
Tremolite	14567-73-8	Feed	Rat.
Trichlorfon	52-68-6	Feed	Rat/mouse.
1,1,1-Trichloroethane	71-55-6	Gavage	Rat/mouse.
Trichloroethylene	79-01-6	Gavage	Rat/mouse.
Tris(2-ethylhexyl)phosphate	78-42-2	Gavage	Rat/mouse.

Table 7.—*Chemicals Being Tested in Fiscal Year 1979 Using Carcinogenesis Bioassays—Continued*

Chemical	CAS No.[1]	Route	Species
4-Vinylcyclohexane	100-40-3	Gavage	Rat/mouse.
Vinylidene chloride	75-35-4	Gavage	Rat/mouse.
Vinyl toluene	1319-37-5	Inhal.	Rat/mouse.
Violet 3	1325-82-2	Feed	Rat/mouse.
Witch hazel	84400-12-7	SP	Rat/mouse.
Yellow #14	842-07-9	Feed	Rat/mouse.
Xylene sulfonic acid, sodium salt	1300-72-7	Feed	Rat/mouse.
Zearalenone	7645-23-0	Feed	Rat/mouse.
Ziram	137-30-4	Feed	Rat/mouse.

[1] Chemical Abstract Service Registry Number.

Table 8.—*Chemicals for Which Carcinogenesis Bioassays Were Completed[1] in fiscal year 1979[2]*

Chemical	CAS No.[3]	Technical report No.[4]	Carcinogenicity test results
Aldicarb	116-06-3	136	Negative.
Allyl chloride	107-05-1	73	Suspect.
2-Aminoanthraquinone	117-79-3	144	Positive.
3-Amino-9-ethylcarbazole hydrochloride	132-32-1	93	Positive.
1-Amino-2-methylanthraquinone	82-28-0	111	Positive.
4-Amino-2-nitrophenol	119-34-6	94	Positive.
Anilazine	101-05-3	104	Negative.
Aniline hydrochloride	142-04-1	130	Positive.
p-Anisidine hydrochloride	20265-97-8	116	Negative.
Azinphosmethyl	86-50-0	60	Suspect.
Azobenzene	103-33-3	154	Positive.
Butylated hydroxytoluene (BHT)	128-37-0	150	Negative.
Calcium cyanamide	156-62-7	103	Negative.
Carbromal	77-65-6	170	Negative.
4'-(Chloroacetyl)acetanilide	140-49-8	177	Negative.
p-Chloroaniline	106-47-8	159	Suspect.
Chlorobenzilate	510-15-6	75	Positive.
(2-Chloroethyl)trimethylammonium chloride	999-81-5	158	Negative.
2-(Chloromethyl)pyridine hydrochloride	6959-47-3	178	Negative.
3-(Chloromethyl)pyridine hydrochloride	7099-45-4	95	Positive.
3-Chloro-p-toluidine	95-74-9	145	Negative.
2-Chloro-p-phenylenediamine sulfate	61702-44-1	113	Negative.
5-Chloro-o-toluidine	95-79-4	167	Positive.
4-Chloro-o-toluidine hydrochloride	3165-93-3	165	Positive.
Chlorothalonil	1897-45-6	41	Positive.
C. I. Vat Yellow 4	128-66-5	134	Positive.
Clonitralid	1420-04-8	91	Negative.
Coumaphos	56-72-4	96	Negative.
p-Cresidine	120-71-8	142	Positive.
Cupferron	135-20-6	100	Positive.
2,4-Diaminotoluene	95-80-7	162	Positive.
Diazinon	333-41-5	137	Negative.
Dibenzo-p-dioxin	262-12-4	122	Negative.
1,2-Dibromoethane	106-93-4	86	Positive.
Dibutyltin diacetate	1067-33-0	183	Negative.
2,7-Dichlorodibenzo-p-dioxin (DCDD)	33857-26-0	123	Suspect.
Dichlorodiphenylethane (p,p'-DDE)	72-55-9	131	Positive.
Dichlorodiphenyltrichloroethane (DDT)	50-29-3	131	Negative.
Di(p-ethylphenyl)dichlorothane (p,p'-Ethyl-DDD; Perthane)	72-56-0	156	Suspect.
N,N'-Diethylthiourea	105-55-5	149	Positive.
2,4-Dimethoxyaniline hydrochloride	54150-69-5	171	Negative.
3,3'-Dimethoxybenzidine-4,4'-diisocyanate	91-93-0	125	Positive.
Dimethylterephthalate	120-61-6	121	Negative.
Dioxathion	78-34-2	125	Negative.
Endrin	72-20-8	12	Negative.
Ethyl tellurac	20941-65-5	152	Positive.
Fenthion	30145-35-1 55-38-9	103	Suspect.
Formulated fenaminosulf	140-56-7	101	Negative.
Iodoform	75-47-8	110	Negative.
Lead dimethyldithiocarbamate	19010-66-3	151	Negative.
Lithocholic acid	434-13-9	175	Negative.
Malaoxon	1634-78-2	135	Negative.
dl-Menthol	89-78-1	98	Negative.
Methyl parathion	298-00-0	157	Negative.
Mexacarbate	315-18-4	147	Negative.
Michler's ketone	90-94-8	101	Positive.
1,5-Naphthalenediamine	2243-62-1	143	Positive.
N-(1-Naphthyl)ethylenediamine dihydrochloride	1465-25-4	160	Negative.
5-Nitroacenaphthene	602-87-9	118	Positive.
3'-nitro-p-acetophenetide	1777-84-0	133	Suspect.
5-Nitro-o-anisidine	99-59-2	127	Positive.
4-Nitroanthranilic acid	619-17-0	109	Negative.
6-Nitrobenzimidazole	94-52-0	117	Positive.
Nitrofen	1836-75-5	184	Positive.
2-nitro-p-phenylenediamine	5307-14-2	169	Positive.
4-Nitro-o-phenylenediamine	99-56-9	180	Negative.
N-nitrosodiphenylamine	86-30-6	164	Positive.
p-Nitrosodiphenylamine	156-10-5	190	Positive.
beta-Nitrostyrene and styrene	100-42-5, 102-96-5	170	Negative.

Table 8.—*Chemicals for Which Carcinogenesis Bioassays Were Completed[1] in fiscal year 1979[2]—Continued*

Chemical	CAS No.[3]	Technical report No.[4]	Carcinogenicity test results
Phenazopyridine hydrochloride	136-40-3	58	Positive.
p-Phenylenediamine dihydrochloride	624-18-0	174	Negative.
1-Phenyl-3-methyl-5-pyrazolone	89-25-8	141	Negative.
1-Phenyl-2-thiourea	103-85-5	148	Negative.
Phosphamidon	13171-21-6	16	Negative.
Phthalamide	88-96-0	161	Negative.
Phthalic anhydride	85-44-9	150	Negative.
Piperonyl butoxide	51-03-6	120	Negative.
Piperonyl sulfoxide	120-62-7	124	Positive.
Pivalolactone	1955-45-9	140	Positive.
Procarbazine hydrochloride	366-70-1	19	Positive.
p-Quinone dioxime	105-11-3	179	Positive.
Sodium diethyldithiocarbamate	148-18-5	172	Negative.
Styrene	100-42-5	185	Suspect.
Sulfallate	95-06-7	115	Positive.
Sulfisoxazole	127-69-5	136	Negative.
Tetrachlordiphenylethane (TDE)	72-54-8	131	Suspect.
2,3,5,6-Tetrachloro-4-nitroanisole	2435-53-2	114	Negative.
Tetraethylthiuram disulfide	97-77-8	156	Negative.
Titanium dioxide	13463-67-7	97	Negative.
2,5-Toluenediamine sulfate	6369-59-1	134	Negative.
o-Toluidine hydrochloride	636-21-5	153	Positive.
2,4,6-Trichlorophenol	88-06-2	155	Positive.
2,4,5-Trimethylaniline	137-17-7	160	Positive.
Trimethylthiourea	2489-77-2	179	Positive.
Triphenyltin hydroxide	76-87-9	130	Negative.

[1] When announced in the FEDERAL REGISTER.

[2] Certain chemicals were not listed in the NTP Annual Plan for FY 1979 because they were started on test prior to NTP establishment.

[3] Chemical Abstract Service Registry Number.

[4] Available from Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20205.

Table 9.—*Chemicals for Which Carcinogenesis Bioassays Will Be Completed[1] In fiscal year 1980*

Chemical	CAS No.[2]	Route	Species
Agar agar	9002-18-0	Feed	Rat/mouse.
Aminoundecanoic acid	27323-47-3	Feed	Rat/mouse.
Asbestos, amosite	12172-73-5	Feed	Rat/hamster.
Asbestos, chrysotile SR	12001-29-5	Feed	Rat/hamster.
Asbestos, chrysotile IR	12001-29-5	Feed	Rat/hamster.
Benzoin	119-53-9	Feed	Rat/mouse.
Bis(2-chloro-1-methylethyl) ether	108-60-1	Gavage	Rat/mouse.
Bisphenol A	80-05-7	Feed	Rat/mouse.
Butyl benzyl phthalate	85-68-7	Feed	Rat/mouse.
Caprolactam	105-60-2	Feed	Rat/mouse.
Cinnamyl anthranilate	87-29-6	Feed	Rat/mouse.
Cytembena	2126-70-7	IP/IJ	Rat/mouse.
D & C red no. 9	5160-02-1	Feed	Rat/mouse.
1,4-Diamino-2,6-dichlorobenzene	609-20-1	Feed	Rat/mouse.
Dibromochloropropane	96-12-8	Inhal.	Rat/mouse.
1,2-Dibromoethane	106-93-4	Inhal.	Rat/mouse.
Di(2-ethylhexyl)adipate	103-23-1	Feed	Rat/mouse.
Di(2-ethylhexyl)phthalate	117-81-7	Feed	Rat/mouse.
Disperse yellow #3	2832-40-8	Feed	Rat/mouse.
Eugenol	97-53-0	Feed	Rat/mouse.
Fluometuron	2164-17-2	Feed	Rat/mouse.
Guar gum	9000-30-0	Feed	Rat/mouse.
Gum arabic	9000-01-5	Feed	Rat/mouse.
Gum tara	39300-88-4	Feed	Rat/mouse.
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin	57653-85-7	SP	Mouse.
		Gavage	Rat/Mouse.
Locust bean gum	9000-40-2	Feed	Rat/Mouse.
Malathion	121-75-5	Feed	Rat.
Mannitol	69-65-8	Feed	Rat/Mouse.
4,4'-Methylenebus (N,N-dimethyl) aniline	101-61-1	Feed	Rat/Mouse.
Mirex	2385-85-5	Feed	Rat.
Orange #10	1936-15-8	Feed	Rat/Mouse.
4,4'-Oxydianiline	101-80-4	Feed	Rat/Mouse.
Phenol	108-95-2	Water	Rat/Mouse.
Red #14	3567-69-9	Feed	Rat/Mouse.
Reserpine	50-55-5	Feed	Rat/Mouse.
Selenium sulfide	7488-56-4	Gavage	Rat/Mouse.
		SP	Mouse.
Selsun (Commerical)	UNK	SP	Mouse.
Sunset Yellow FCF #6	2783-94-0	Feed	Rat/Mouse.
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1746-01-6	Gavage	Rat/Mouse.
		SP	Mouse.
1,1,1,2-tetrachloroethane	630-20-6	Gavage	Rat/Mouse.
Toluene, 2,6-diamine dihydrochloride	823-40-5	Feed	Rat/Mouse.
Vinylidene chloride	75-35-4	Gavage	Rat/Mouse.
Yellow #14	842-07-9	Feed	Rat/Mouse.
Ziram	137-30-4	Feed	Rat/Mouse.

[1] When announced in the FEDERAL REGISTER.

[2] Chemical Abstract Service Registry Number.

A lifetime bioassay in rodents is the current procedure utilized to determine carcinogenic potential of a chemical. The NTP does not propose alternative methods but acknowledges a need to develop or validate less expensive and more rapid methods that may prioritize or in some instances supplant the need for lifetime bioassays.

In vitro mammalian cell transformations are potential short-term assays for indicating carcinogenic potential of a chemical. Transformation assays being evaluated include BALB/c 3T3, Fischer Rat Embryo (RLV infected), hamster embryo, and C3H 10T½. In FY 79, tests on 31 chemicals were initiated in hamster embryo clonal assays and the BALB/c 3T3 focus assay (Table 12). These chemicals were selected based on the existence of adequate lifetime carcinogenesis bioassays and mutagenicity data derived from standardized *Salmonella* assays. This validation initiative will be completed in FY 80.

A testing program that permits comparison of standardized *Salmonella* assay results with lifetime rodent bioassays is described in the Genetic Toxicology section.

The mouse lung adenoma model is proposed as an *in vivo* system for determining carcinogenic potential of a chemical in a relatively short period of time. Lung adenomas are indigenous in aging strain A mice. Treating this strain with many drugs and selected environmental contaminants found to be carcinogenic in other models has shortened the period of tumor occurrence and increased the number of adenomas in a dose related fashion. Conclusions similar to those obtained from the lifetime bioassay were obtained with this model for over 70 percent of a limited number of chemicals. In FY 79 a project plan was completed that will evaluate and validate lung adenoma occurrence in the strain A mouse as a model for screening and prioritizing candidate test chemicals. Sixty chemicals previously tested in lifetime bioassays will be tested in the strain A mouse during FY 80 and an additional 30 chemicals in FY 81. In a parallel study, tests are also planned to assure reproducibility of results and to expand the scope of the model.

Carcinogenesis

During fiscal year 1979, the National Toxicology Program was testing 201 chemicals for carcinogenic potential in lifetime rodent bioassays (Table 7). Of these, 79 chemicals were started on bioassay in FY 79. During the year, tests were completed and reports issued on 95 chemicals (Table 8); under the conditions of the tests, 47 (49.5%) were considered negative, 39 (41%) positive, and 9 (9.5%) suspect carcinogens. Reports of 44 of these chemicals are scheduled for issuance in FY 80 (Table 9). Dependent upon actual resource availability and allocation, testing on 75 chemicals will be initiated in FY 80. Those 41 chemicals previously selected by NTP are listed in Table 10. Another 41 chemicals have been nominated for possible long term carcinogenicity testing (Table 11).

TABLE 10.—Chemicals Scheduled To Start the Carcinogenesis Bioassay in FY 1980

Compound	CAS No.*
Butyl nitrite	544-16-1
Caffeine	58-08-2
Capsaicin	404-86-4
Carbon disulfide	75-15-0
Chloramine	55-86-7
Chloroacetophenone	532-27-4
Chlordecone (Kepone)	143-50-0
p-Chloroaniline	106-47-8
Chlorobenzalmalononitrile	2698-41-1
Cineol (Eucalypto)	470-67-7
Cinnamaldehyde	104-55-2
Dichlorvos	62-73-7
DMBA/TPA (positive control)	57-97-6
Epiephrine hydrochloride	55-31-2
1,2-Epoxybutane	106-88-7
Ethyl alcohol	64-17-5
Ethyl benzene	100-41-4
Ethyl bromide	74-96-4
Ethyl chloride	75-00-3
Ethylene oxide	75-21-8
Formaldehyde	50-00-0
Hexafluoroacetone	10057-27-9
5-Hydroxytryptophan	56-69-9
Isopropyl glycidyl ether	4016-14-2
Mercaptobenzothiazole	149-30-4
5-Nitro-2-furaldehyde	698-63-5
Ochratoxin	37203-43-3
Oil of nutmeg	8008-45-5
Pentachloroanisole	1825-21-4
Pentachloronitrobenzene	82-68-8
Polyurethane	9009-54-5
Pyrrolizidine alkaloids	643-20-9
Roxarsone	121-19-7
Sucrose	25702-74-3 9012-95-7 27616-49-5
2,3,7,8-Tetrachlorodibenzofuran	51207-31-9
Tetracycline hydrochloride	64-75-5
Tocopherol	1406-66-2
Toluene	108-88-3
Trimellitic anhydride	552-30-7
Wollastonite calcium-silicates	13983-17-0
Xylenes, mixed (commercial)	1330-20-7

* Chemical Abstract Service Registry Number.

TABLE 11.—Chemicals Nominated for Carcinogenesis Bioassays

Compound	CAS No.*
Benzaldehyde	100-52-7
Benzilic acid, 4,4'-dichloroethyl ester	510-15-6
gamma-Butyrolactone	96-48-0
Catechol	120-80-9
Chlorinated naphthalenes	—
Chromium (metal)	7440-47-3
Curcumin	458-37-7
2,4-Diaminophenol dihydrochloride	137-09-7
1,1-Dichloroethylene (Vinylidene chloride)	75-35-4
Dichloropropane	26638-19-7
Diethyl phthalate	84-66-2
3,4-Dihydrocoumarin	119-84-6
Dimethoxane	828-00-2
Ethylene glycol	107-21-1
Furfural	98-01-1
Furfuryl alcohol	98-00-0
H C yellow no. 4	52561-67-4
Hexachlorocyclopentadiene	77-47-4
Hexachloroethane	67-72-1
4-Hydroxyacetanilide	103-90-2
Isoproterenol hydrochloride	51-30-9
Lead dioxide	1309-60-0
o-Methylhydroxylamine	67-62-9
Monosodium methane arsenate	2163-80-6
Nitrobenzene	98-95-3
p-Nitrophenol	100-02-7
N-Nitrosodiethanolamine	1116-54-7
Pentaerythritol tetranitrate	78-11-5
N-Phenylhydroxylamine	100-65-2
Probenecid	57-66-9
Quercetin	522-12-3
p-Quinone	106-51-4
Resorcinol	108-46-3
Sodium azide	26628-22-8
Tellurium	13494-80-9
Titanium ferrocene	1271-19-8
2,4,6-Trinitrotoluene	118-96-7
Tris (2-chloroethyl) phosphate	115-96-8
Vinyl cyclohexene dioxide	4223-10-3
Xylenesulfonic acid, sodium salt	1300-72-7
2,6-Xylidine	87-62-7

* Chemical Abstract Service Registry Number.

TABLE 12.—Chemicals Being Tested in Cell Transformation Assays

Chemical	CAS No.*
Aldicarb	116-06-3
Aniline hydrochloride	142-04-1
o-Anisidine hydrochloride	134-29-2
4-Amino-2-nitrophenol	119-34-6
2-Amino-5-nitrothiazole	121-66-4
Aspirin	50-78-2
Aspirin, phenacetin, and caffeine	8003-03-0
1,2,3-Benzotriazole	95-14-7
Caffeine	58-08-2
p-Chloroaniline	106-47-8
3-Chloromethylpyridine hydrochloride	6959-48-4
Cinnamyl anthranilate	87-29-6
tris-(2,3-Dibromopropyl) phosphate	126-72-7
N,N'-Dicyclohexylthiourea	1212-29-9
1,3-Dichloro-5,5'-dimethylhydantoin	118-52-5
4,4'-bis(Dimethylamino) benzophenone	90-94-8
Dyrene (anilazine)	101-05-3
Ethylene dibromide	106-93-4
Fluometuron	2164-17-2
Lithocholic acid	434-13-9
4,4'-Methylenebis(N,N'-dimethylaniline)	101-61-1
1,5-Naphthalenediamine	2243-62-1
Nitrilotriacetic acid (trisodium salt monohydrate	18662-53-8
4-Nitro-o-phenylenediamine	99-56-9
2-Nitro-p-phenylenediamine	5307-14-2
3-Nitropropionic acid	504-88-1
Phenacetin	62-44-2
p-Phenylenediamine	106-50-3
Proflavin hydrochloride	952-23-8
Reserpine	50-55-5
Styrene	100-42-5

* Chemical Abstract Service Registry Number.

During FY 80, the appearance of precursor (preneoplastic) liver lesions in hepatectomized rats treated with carcinogens will be evaluated as a potential *in vivo* model for predicting carcinogeneses at an early stage.

Carcinogenicity testing traditionally begins with young adult animals (typically six-week old rodents). However, human chemical exposures may include the period of *in utero* development and infancy, as well as continued lifetime exposure. These exposures occur through exposure of pregnant workers, use of drugs, and long-term accumulation and persistence

of certain chemicals in the mother's body with secretion in milk. The adequacy of lifetime bioassay methods as opposed to methods that also include prenatal and neonatal exposures in being evaluated. Four chemicals are being tested: a polybrominated biphenyl, phenytoin (diphenylhydantoin), ethylene thiourea, and chlordecone (a chemical with estrogenic properties).

Inhalation bioassays for carcinogenicity usually involve a duration of exposure that is arbitrarily determined. The specialized facilities required for inhalation studies are expensive and commit scarce technical manpower for extended periods of time. Studies with mice, rats, and hamsters are in progress that use a design which varies the age of animals exposed and the duration of exposure to vinyl chloride, a known carcinogen. The objective is to provide data that permit a species comparison of tumor response and an analysis of the exposure regimens that provide a predicted carcinogenic response. The data may indicate that a period of exposure of less duration than is currently employed will provide a meaningful bioassay result. These studies are projected for completion in FY 80.

Chemical Disposition

Developing knowledge about the absorption, distribution, metabolism, and excretion of chemicals selected for testing remains a major objective of NTP. Information necessary for the proper design and interpretation of toxicology and carcinogenicity studies includes knowing whether a chemical accumulates in the body, causes toxic effects directly or through formation of a metabolite, whether these events occur only at certain dose levels of if there is a species difference in the pathways or rate of chemical disposition.

Resources available to NTP in FY 79 were principally through two university contracts, with capability to be enhanced in FY 80 through the recruitment of two scientists to the NTP intramural component and expansion of contract capability from two to four laboratories. This will permit 12–15 chemicals to be studied in FY 80 with capability increased to 24 by the end of the year.

For the most efficient use of limited capability, preference in selection of work is toward development of a core of knowledge based on chemical class characteristics that can be used to predict the disposition of new chemicals within that class or in chemically related classes. Studies on three major chemical classes were initiated or continued under NTP in FY 79: halogenated polyaromatics, benzidine based dyes and haloalkyl phosphates.

Studies of halogenated polyaromatics include evaluation of the disposition of several polychlorinated biphenyls (PCBs), a chlorodibenzodioxin, a chlorodibenzofuran, and a chlorinated azobenzene. Comparative studies of the disposition of selected PCBs have been conducted in the rat, dog, and monkey. The results of thse studies demonstrate that the half-life of a given PCB in a given species is dependent upon the capacity of that species to metbolize the PCB to a major polar compound which can be excreted. Species vary widely in ability to metabolize PCBs and the species studied are ranked as follows: dog> rat>> monkey. Excretion of unchanged PCBs prior to metabolism is negligible in all species studied. Current work is devoted toward identifying metabolities and establishing the disposition pattern of 3,3',4,4'-tetrachlorobiphenyl, one of the more toxic PCBs in the rhesus monkey. These studies, to be completed in FY 80, may provide information that advances our ability to interpret the public health significance of PCB toxicology data from several animals species.

Information about the chemical disposition of chlorodibenzodioxins is based primarily of 2,3,7,8–TCDD. This knowledge base will be expanded in FY 80 through study of octachlorodibenzodioxin, the chemically related 2,3,7,8-tetrachlorodibenzofuran, and the sterochemically related 3,4,3,',4'-tetrachloroazobenzene. Comparative species assessment will be performed using the rat, guinea pig, and monkey.

The benzidine dye studies are designed to determine whether the biological conversion of benzidine based dyes (as well as o-tolidine and dianisidine based dyes—chemical congeners representative of chemically related classes) to the free precursors benzidine, o-tolidine, and dianisidine, which are carcinogens, is a general phenomenon. Thirteen dyes are being studied in the dog and will be completed in the first quarter of FY 80 (Table 13). Interim results indicate that conversion of benzidine based dyes to benzidine and the excretion of benzidine in the urine is a generalized phenomenon which will occur after administration or exposure to benzidine based dyes.

The haloalkyl phosphates include a number of fire retardants and insecticides. Two of these compounds, tris (1,3-dichloroisopropyl) phosphate ("Fyrol FR–2") and tris (2,3-dibromopropyl) phosphate ("Tris") are being studied to determine if these structurally related haloalkyl phosphates which vary in their mutagenic potential, follow similar patterns of tissue distribution, metabolism, excretion, and covalent binding.

A continuing priority of chemical disposition studies under NTP is the extrapolation of laboratory data to humans. One way is to develop *in vitro* animal and human cell cultures that proportionally reflect *in vivo* metabolism to facilitate a more accurate extrapolation of chemical metabolism information from animals to humans. The initial *in vitro* systems to be developed use tissues from rats, dogs and monkeys.

TABLE 13.—Chemical Disposition; List of Benzidine, o-Tolidine and Dianisidine Based Dyes Under Study

	CAS No.*
Benzidine Based Dyes:	
Direct Black 4	2429–83–6
Direct Blue 2	2429–73–4
Direct Brown 2	2429–82–5
Direct Green 1	3626–28–6
Direct Orange 1	54579–28–1
Direct Orange 8	2429–79–0
Direct Red 28	573–58–0
o-Tolidine Based Dyes:	
Acid Red 25	
Direct Red 2	992–59–6
Direct Red 39	
Dianisidine Based Dyes:	
Direct Blue 1	2610–05–1
Direct Blue 15	2429–74–5
Direct Blue 218	28407–37–6

*Chemical Abstract Service Registry Number.

General Toxicology

Prior to conducting and interpreting any specialized experiments in carcinogenesis, reproductive toxicology, teratology, or neurobehavioral toxicology, the effect of the chemical on the general health of the test animal must be known. During FY 80, studies will continue to develop a toxicologic screen that will identify vital organ damage (hepatic, renal) which results in a generalized toxicity and one that gives presumptive evidence of specific toxicities relating to fertility and reproduction, neurobehavioral toxicology, and immunology. The screen will also establish the range of doses over which toxicities occur, variability of toxicity between males and females in rates and mice, and in certain instances will establish the basic disposition pattern of a chemical as a function of dose and time. Presumptive evidence of specific toxicity then will be studied by scientists who are specialists in that area.

NTP is also attempting to identify and develop more sensitive methods for detection of injury to hepatic and renal function. Renal toxicity methods being reviewed and validated include kidney functions such as concentrating ability

and excretion rate of major nephron segments as well as early indicators for cellular damage such as the presence of selected intracellular enzymes in urine.

Immunologic Toxicology

NTP is committed to studies that establish the role of immune assessment in toxicologic characterization of chemicals. The immunologic functions to be used in a test battery were reviewed in FY 79 with six parameters selected: (1) *In vitro* lymphocyte response to mitogens; (2) *In vitro* macrophage function; (3) Antibody response to a T&B cell dependent antigen; (4) Delayed hypersensitivity; (5) Host resistance; and (6) Sensitivity to endotoxin. In some instances the preferred method to assess a specific immunologic function can only be determined through a comparison of methods. Research on methods selection will continue in NTP laboratories with validation and interlaboratory comparison of methods through contracts awarded in FY 80. An interim immunology test battery is being selectively used in the NTP toxicology screen. Methods for indepth characterization of immunosupression are also being developed in NTP laboratories, and a framework is being developed for collaborative studies with selected chemicals among NTP laboratories.

Neurobehavioral Toxicology

Laboratories within the NTP are actively engaged in the development of new methods and in validation of existing methods for testing the neurologic and behavioral effects of chemicals.

A previously developed standardized test battery is being validated by evaluating the effects of nine neurotoxic chemicals: (1) acrylamide, (2) d-amphetamine, (3) arsenic trioxide, (4) chlordecone, (5) lead acetate, (6) methyl mercury, (7) polychlorinated biphenyl, (8) sodium salicylate, and (9) triethyl tin. The two objectives are: (1) To determine the ability of neurobehavioral procedures to detect an unexpected neurotoxic effect and to ascertain the capability of each test to provide an expected negative result; and (2) To generate a profile of effects for each substance so that tests assumed to measure the same or similar functions can be compared for relative sensitivity. The test battery includes methods that assess sensory function, motor strength and coordination, associative or cognitive factors, or emotionality.

An interim neurobehavioral test battery will also be selectively utilized in the NTP toxicology screen. A test capability for more extensive characterization of six chemicals/year associated with neurobehavioral toxicity is to be developed by contract in FY 80. Extensive characterization of the neurobehavioral toxicity of chlordecone, in response to the public health concerns of the state of Virginia, is being performed in NTP laboratories. These studies include the description and the persistence of effects in adult rats and in rats exposed during development.

Pulmonary Toxicology

Toxicity testing of inhaled materials rarely includes an assessment of pulmonary function. In recent years a number of techniques have been developed that measure indices of pulmonary function in rodents—static lung volumes, static and dynamic lung properties, diffusion, and information about the distribution of ventilation. The applicability of these measurements in the assessment of pulmonary toxicity as well as their sensitivity compared to pathologic evaluation of lung damage remains to be demonstrated. Through contract agreements NTP has initiated a series of studies centered around a comprehensive comparison of morphologic change versus functional change to validate the usefulness of respiratory physiology techniques. Six compounds are to be evaluated in the rat and hamster at three dose levels during FY 80 and 81.

Reproductive and Developmental Toxicology

Fertility and reproduction are major areas that require toxicologic methods development and testing. Because these are areas in which personnel and resources available to NTP are in short supply, innovative methods development is not proposed, and efforts will be confined to test procedures that are within the capabilities of general toxicologists.

Teratology plans in FY 80 represent a continuation of progams outlined in FY 79: (1) Evaluation of chemicals for which there is definitive human and animal teratology data to insure that all data are being most effectively utilized; (2) Examination of existing laboratory data to determine the range of dose parameters that indicate linearity of response and permit identification of biomathematical proedures for low dose risk estimation; and (3) Histopathologic examination of fetuses for comparison with traditional methods to determine the adequacy of current methodology.

Testing of chemicals for teratogenic effects will continue at a rate of 8–10 per year. Chemicals for which teratology testing is in progress are ethylene chlorhydrin, ethylene oxide, formaldehyde, pentachloroanisole, toluene, and the xylenes. Results are scheduled to be reported in FY 80 (Table 14). Five additional chemicals have been selected for testing: caffeine, dimethylaniline, ethoxy ethanol, lead monoxide, and 2,3,7,8-tetrochlorodibenzofuran.

Table 14.—*Chemicals Reported, Testing in Progress or Selected for Teratology Assays—FY 1980*

Chemical	CAS No.[1]	Species	Route
Reported in FY 80			
Ethylene Chlorohydrin	107-07-3	Mouse, rabbit	I.V.
Ethylene Oxide	75-21-8	Mouse, rabbit	I.V.
Formaldehyde	50-00-0	Mouse	Oral.
Pentachloroanisole	1825-21-4	Mouse	Oral.
Toluene	108-88-3	Mouse	Oral.
Xylene, mixed (Commercial)	1330-20-7	Mouse	Oral.
o-Xylene	95-47-6	Mouse	Oral.
m-Xylene	108-38-3	Mouse	Oral.
p-Xylene	106-42-3	Mouse	Oral.
Selected for Testing			
Caffeine	58-08-2		
Dimethylaniline	87-62-7		
Ethoxy Ethanol	110-80-5		
Lead Monoxide	1317-36-8		
2,3,7,8-Tetrachlorodibenzofuran	51207-31-9		

[1] Chemical Abstract Service Registry Number.

Incidence of behavioral disorders and learning deficits observed in children, together with the demonstration of behavioral dysfunctions in animals following prenatal exposure to a variety of chemicals suggests the need for behavioral evaluation of neonates in the safety assessment of new drugs and chemicals. Incorporation of behavioral

evaluation into testing guidelines should be determined after reviewing data that have been produced under standardized and validated test conditions. The behavioral teratology * initiative is to identify and develop screening methods which: (1) Yield valid and reproducible results within and among laboratories; (2) Are sensitive to toxic alterations produced by a range of agents of varying toxic potential; (3) Are predictive of toxic effects in humans; and (4) Are cost efficient.

In FY 79 a test protocol was developed and studies initiated that will standardize these tests for the reliability and sensitivity of six behavioral methods using three chemicals known to cause behavioral teratogenic effects—Vitamin A, methyl mercury, and d-amphetamine. The planned activities for FY 80 are to conduct pilot studies, select six laboratories to conduct the studies, and begin the test validation experiments.

Coordinative Management Activities

A process for nominating, evaluating, and selecting chemicals was initiated in FY 79 which is detailed below and in Figure 4.

Chemical Nomination

1. The Program Director requests from each participating agency and from other Federal and non-government sources a priority list of chemical candidates for testing in the NTP.

2. All nominations are submitted to the Chairman, NTP Chemical Nomination Group.

3. Each nomination must be supported with relevant information, including:

a. Chemical Identification and Properties:

(1)Identification (single chemicals).

(2) Physical and Chemical Properties.

(3) Commercial Product Composition.

(4) Exposure-related Information and Production and Use.

(5) Environmental Surveillance.

b. Toxicity:

(1) Human Data.

(2) Animal Tests and Information.

(3) *In vitro* and other Short-term Tests.

c. Metabolism Studies and Structure-Activity Considerations:

(1) Pharmacokinetic Data and Metabolic Pathways.

(2) Structure-Activity Correlations and Considerations.

d. Ongoing Toxicological or Environmental Studies in the Government and/or Private Sector.

e. Rationale for Choice of Recommended Chemical for NTP and Suggested Studies to be Undertaken.

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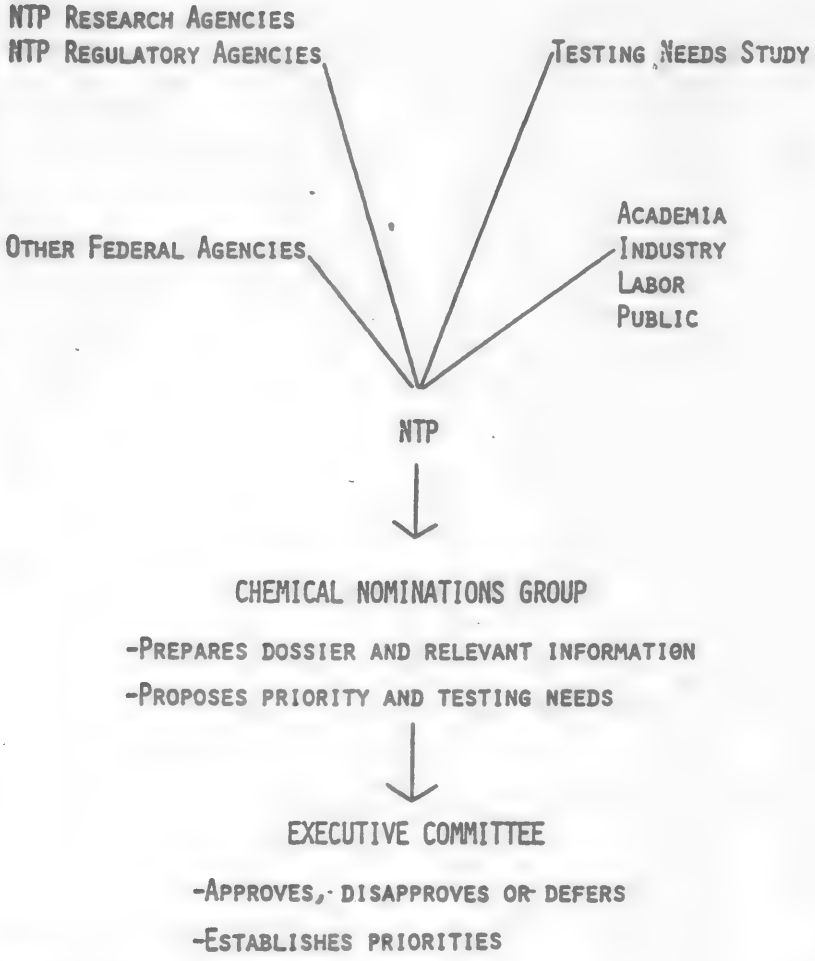
* The term "behavioral teratology" is somewhat of a misnomer. It refers to effects on behavior during animal development resulting from prenatal exposure to chemicals.

FIGURE 4

CHEMICAL NOMINATION AND SELECTION PROCESS



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Chemical Evaluation

1. The NTP Chemical Nomination Group—comprising representatives from EPA, OSHA, FDA, CPSC, NIH, NCI, NIEHS, NIOSH, and NTP—will determine if each chemical nomination qualifies according to the Principles for Chemical Selection.

2. This group will develop a dossier containing relevant information on chemical properties, production, use, exposure, and toxicology data. It will prepare a summary for each nomination that proposes toxicologic testing needs.

Chemical Selection

Critical to the effective long-term operation of the NTP Program is the chemical nomination and selection process. This process has recently been reviewed by several committees and recommendations are stated below. NTP will initiate in FY 80 a "Testing Needs Study." The purpose of this effort is to estimate the number of compounds to which a significant number of people are exposed but which are untested, inadequately tested, or raise suspicions in one or more toxicological parameters. With this information, better projections can be made about chemicals that need testing over the next several years.

During the course of this study, a large number of compounds will be reviewed for both human exposure and toxicologic potential and this review will identify compounds that should be tested. Although this study will take at least two years to complete, useful information will be produced as the study progresses.

The two primary decision areas for testing of a chemical are the chemical, physical and toxicological properties of the chemical and the extent of human and environmental exposure to the chemical. Unfortunately, for too many chemicals, little is known about either of these areas.

Information on the chemical in question includes physical properties that determine whether the chemical is volatile, or soluble in certain media, etc. Important chemical characteristics such as stability in the environment are also part of the dossier as is the fate in various media where biological activity may alter the chemical structure and produce different products. Also considered are metabolic alterations and storage as well as bioconcentration in the food chain. This kind of information is frequently available in part or can be obtained to serve as an adequate basis for further decision making.

Toxicological data on the chemical are usually not available or may be incomplete. In these situations the chemical must be judged for potential toxicological parameters on the basis of its structure and relationship to other chemicals of similar structure for which toxicological data are already available. These groups of chemicals to which the one under consideration is compared must be a close relative and careful comparisons are imperative. The development and validation of short-term tests will allow NTP eventually to screen cheaply and rapidly many more of these untested chemicals so that those most likely to be toxic can be targeted for more extensive (and expensive) testing.

Besides these major considerations of the intrinsic chemical and physical properties of the compound under study, investigative research must be carried out on possible impurities which may be present in the final product or which may be formed on use or misuse of the chemical.

The extent of human exposure is the second area which needs assessment for setting priorities. The information may be more readily available than that for the intrinsic properties of the chemical. Figures on production, industrial processing, and waste material from processing are necessary to judge the potential for exposure of people in the work place, or the contamination of the air, water, soil or food by the chemical. This information is most often not available and is not easy to locate. Exposure use may or may not involve the general population and final disposal of the material also needs to be known.

A composite exposure figure is extremely difficult to assemble since in the environment the chemical may have changed its structure or composition. The metabolite(s) may contribute to the toxicological effects of the chemical. Thus, for many highly toxic chemicals, information to be gathered must deal with the altered derivatives as well.

The Executive Committee has developed and approved a set of principles for chemical selection which states:

The NTP Executive Committee operates under the principle that industry will test chemicals for health and environmental effects as intended and mandated by the Congress under legislative authorities. Therefore, the NTP, acting under its chemical selection principles, will test:

1. Chemicals found in the environment that are not closely associated with commercial activities;

2. Desirable substitutes for existing chemicals, particularly therapeutic agents, that might not be developed or tested without Federal involvement;

3. Chemicals that should be tested to improve scientific understanding of structure-activity relationships and thereby assist in defining groups of commercial chemicals that should be tested by industry;

4. Certain chemicals tested by industry, or by others, the additional testing of which by the Federal government is justified to verify the results;

5. Previously tested chemicals for which other testing is desirable to cross-compare testing methods;

6. "Old chemicals" with the potential for significant human exposure which are of social importance but which generate too little revenue to support an adequate testing program (some of these may be "grandfathered" under FDA laws);

7. Two or more chemicals together, when combined human exposure occurs (such testing probably cannot be required of industry if the products of different companies are involved); and

8. In special situations, as determined by the Executive Committee, marketed chemicals which have potential for large-scale and/or intense human exposure, even if it may be possible to require industry to perform the testing.

Further, the NTP Executive Committee will select chemicals for NTP testing after receipt and review of the executive summaries submitted by the Chemical Nomination Group. The selection of a chemical does not *a priori* commit the chemical to testing by NTP. But NTP is committed to ascertain the specific toxicologic and regulatory concerns; evaluate the adequacy of existing data or current efforts in government, academic, or private laboratories; and then propose and conduct specific test(s) that are needed. Occasionally new information is obtained that answers the questions posed in the nomination and selection process.

Chemical Management

To insure that each chemical selected for testing is thoroughly evaluated, NTP assigns a Compound Manager to each compound approved for lifetime studies. The Compound Manager follows the chemical through each of the various phases of testing:

Pretesting Phase

Review dossier
Identify chemical form
Design protocol
Ensure that protocol satisfies needs of nominating agencies
Clear protocol with NTP Protocol Review Committee
Determine availability, purity, etc., of compounds

Study Phase

Ensure protocol is being followed
Monitor study for unexpected findings
Prepare draft monograph on the compound

Review and Report Phase

Review results

Incorporate new results into monograph
Submit monograph, with new results, for peer review

Chemical Repository

A capability for centralized management of chemicals tested by the NTP is needed to characterize and assure the quality of chemicals, thereby minimizing external sources of variability in the testing results.

Contracts will be expanded in scope to provide for procurement, storage, distribution, chemical analysis, purification, synthesis, and reference archiving for approximately 3,000 chemicals. Capabilities will be maintained for analysis of bulk chemicals, chemicals in test vehicles, samples for quality assurance, tissues and fluids, purity and stability determinations, and residual and reprocured chemicals. In addition, the NTP will provide for purification, preparation of derivaties, and routine synthesis of test chemicals.

The NTP will maintain the capability for sophisticated chemical analysis of the chemical and of contaminants in each chemical to be tested. In the Phase I Genetic Toxicology screen such analyses will be performed when toxicologic tests using mixtures or chemicals with impurities are positive, to identify the specific component(s) that may be associated with the toxic effect.

Data Management and Analysis

Data Acquisition

As part of its testing initiative, NTP will develop a substantial amount and variety of data that must be accurately acquired, stored and made promptly available for retrieval at multiple locations. For example, initiating lifetime carcinogenesis bioassays on 75 chemicals each year (which on the average requires 64 months for a report issuance) forecasts that 400 lifetime bioassays must be tracked simultaneously, each of which involves a minimum of 300 animals (thus 120,000) on which data are being gathered at least weekly for 2–2½ years.

The NTP is committed to developing computer operated data management systems that provide for direct entry of data; data from the lifetime bioassays for carcinogens and *in vitro* mutagenicity assays were assigned developmental priority. The modular Toxicology Data Management System (TDMS) developed at NCTR in collaboration with NCI is being adapted for data from lifetime carcinogenesis bioassays. The initial modules are scheduled for installation at three sites in the second or third quarter of FY 80. Installation at other NTP laboratories will ensue in late FY 80 and FY 81. A direct data entry system for *in vitro* mutagenicity tests is progressing with laboratory installation schedules to commence in FY 80. Although computerized systems for general toxicology data are of second priority, prototype development will continue.

Statistical Analysis

A major effort has been devoted to microbial mutagenesis data analysis The previously used Poisson methodology has been shown to be inadequate in accounting for statistical variability for microbial plate count data. Newer techniques are now available. Methods have also been developed for analyzing the fluctuation test in microbial systems that include handling aberrant experimental observations and dose response tests. In FY 80 statistical models for high dose toxicity for microbial plate count data will be studied. Further work on appropriate methods for assessing dose response and aberrant observations in plate count data will be conducted.

During FY 79 statistical research efforts were directed toward an assessment of current statistical testing procedures in toxicology and the development of new procedures where needed. Often appropriate procedures do not exist and, thus, existing procedures are used inappropriately with little or no understanding of the consequences of such actions.

Methods for the analysis of binary response data from teratological studies have received considerable attention and are now fairly well developed. The complications due to presence of litter effects have been taken into account by the use of new methodologies and mathematical models. These methods and others will continue to be evaluated with regard to their operating characteristics.

Chronic carcinogenesis studies will require continued statistical methodology development. This includes competing risk techniques, cause of death assumptions, time-to-tumor models, and simultaneous inferences on multiple sites and types of tumors. Probably the most important new area involves the actual design of the bioassay. Because of the needs for low dose risk estimation, consideration should be given to modifications of dose selection. A balance is needed between the high power of detection associated with high dose studies and low dose information needed for extrapolation methods. Also, prior information from short-term tests and other sources should be used in the bioassay design. Clearly, this is a complicated problem with no immediate solutions. Nevertheless, research work has begun and preliminary results will begin to be realized in FY 80.

Management Information

High priority was given in FY 79 to early development of a system that would provide information on chemicals selected for testing, the nature of the test(s), as well as current and projected test status. A tracking for the chemicals on lifetime bioassays was developed and is in use. The FY 80 plans are to expand this information to all other areas of chemical testing and upgrade this information activity to an "online" capability, first on a local basis and then nationally.

Laboratory Animal and Quality Control

The purpose of this coordinated activity is to develop and maintain animal resources for the NTP testing laboratories that are consistent high quality so that results from the various NTP laboratories can be correlated. Further, standardized husbandry and disease monitoring procedures are being developed and initiated to minimize these factors as compromising variables in test evaluations. Standardized diets have been selected for rodents and will be used in tests initiated in FY 80. The quality control procedures represent the effort of NTP scientists and many national experts.

Plans to commence evaluation of the utility of several isogenic strains of mice in preference to a single strain were not realized due to budget limitations and the prioritization of other program areas in preference to this effort. It still remains an area of need in FY 80.

Although $B_6C_3F_1$ mice and F–344 rats are the principal test species, in some instances test species other than mice and rats are preferred. NTP will begin to evaluate test methods and the predictive utility of such data from non-rodent species for human health to better define the circumstances that dictate the preferred use of other species. Chemical disposition and renal toxicity are examples of two areas where such work is planned.

Laboratory Health and Safety

Because research and testing by the NTP involves potentially hazardous materials, laboratory studies must be conducted in such a manner to eliminate human exposure to or environmental release of the material. Further, all research conducted under the auspices of NTP must conform to all applicable local, state, and Federal statutes relating to occupational health and safety, as

well as those dealing with environmental protection.

Each participating unit of the NTP has developed guidelines for health and safety programs governing research within its purview. These guidelines reflect the direction and needs of each unit, but all have common unifying principles. Each relies on a combination of administrative controls, formalized work practices, engineering controls, and personnel protective equipment to control the potential for exposure to hazardous situations; and each includes a medical surveillance program for research personnel. Examples of these programs include the NIEHS Safety and Health Manual, the NCI Carcinogenesis Bioassay Health and Safety Program, and the NCTR Carcinogen Standards.

Recognition of potential problems associated with hazardous waste disposal, coupled with recent regulatory developments, has stimulated the NTP to examine its existing waste disposal practices, and to define those areas where more resources could be profitably directed.

Operating conditions of the many currently available incinerators are not capable of completely destroying all those chemicals slated for incineration, so some are being stored until incineration performance can be evaluated and upgraded as necessary. To meet this goal, NTP staff are participating in an interagency study to identify incinerator designs that are most suitable to laboratory needs.

Information Generation and Dissemination

The National Toxicology Program must ascertain the toxicology of selected chemicals and assure that results will have regulatory significance. The end product is information—scientific information necessary in deciding societal issues relative to our health and environment. To provide that information, the NTP identified two important aspects: first, information must be disseminated to other scientists so that peer review and feedback assure scientific quality. Second, since the scientific product helps society evaluate identified toxicological risks, information must be disseminated to not only the regulators responsible for protecting against risks, but also to those exposed to the risks. Thus, the NTP will establish and use a coordinated communications network to disseminate toxicological information.

The value of information arising from NTP will depend in part on the quality and timeliness of information received into the program. The NTP will therefore actively seek information from all sources: Federal, state and local governments; trade associations, industry, labor; academia; professional societies and public interest groups; the press; individuals; other countries; and all other interested parties. Information received could include nominations of chemicals to be tested; critique and questions about scientific procedures, policies, priorities, and resource allocations; and any other suggestions for program improvement. To encourage multiple communication, NTP program materials must be disseminated widely and rapidly, and questions answered in a timely manner.

Communication is critical to a successful NTP. While the final NTP product will be information useful to individuals, the first priority for 1980 must necessarily be in areas of management and quality monitoring of the testing program, and in developing and validating the necessary battery of tests so that useful information may be produced. Consequently, some of the planned activities discussed below may not be fully accomplished in 1980.

The NTP program for information generation and dissemination includes: Scientific Coordination and Peer Review; Technical Report Preparation and Dissemination; Interagency Coordination; International Coordination; and Public Awareness and Inquiry Response.

Scientific Coordination and Peer Review

Within DHEW, the NTP coordinates toxicological research and testing activities which encompass test development and test validation, and NTP must remain thoroughly aware of scientific procedures and results produced by other laboratories. Active efforts to know about work in progress and to establish better communication links among investigators worldwide will be pursued with the NTP Board of Scientific Counselors.

The special needs in toxicological research and testing require that a high degree of scientific coordination be developed for information generation and dissemination. For instance, a recognized need exists to better coordinate the development and validation of short-term, inexpensive tests, especially in the area of carcinogenesis. Further, to better utilize the tools of information science, the NTP has entered into a cooperative agreement with the National Library of Medicine (NLM). Many of the on-line services available from the NLM are particularly valuable to the NTP: Chemline, Toxline, Research Projects, Medline, Cancerline, Toxicology Data Bank, Laboratory Animal Data Bank, and RTECS (Registry of the Toxic Effects of Chemical Substances). These and other sources will be used to prepare dossiers on chemicals nominated for test and to design test protocols. Information files on chemicals being tested (NTP Data) will be established and made available via NLM. Also, new information services will be located or developed as needed for toxicology specialties not yet covered adequately in existing systems—for example, topics in this category are neurotoxicology, chemical immunotoxicology, and chemical-chemical interactions.

Formal review of the NTP research will occur at four stages: when chemicals are nominated and selected, when test protocols are designed, when test data have been generated, and when technical monographs have been prepared. *Ad hoc* working groups of experts (consultants and some members of the NTP Board of Scientific Counselors) will peer review technical monographs. In addition to this formal peer review process, the Board of Scientific Counselors will continually oversee the overall NTP research program and encourages informal peer review by the refinement of existing communications channels and the development of new channels.

Technical Report Preparation and Dissemination

Preparation of the reports begins with selection of a chemical for testing and appointment of a compound manager. Each manager is responsible for records management throughout the test.

While experiments are in progress, the chemical manager interacts with other Government agencies and serves as resource person for scientific inquiries concerning the chemical and its possible adverse effects. Lists of chemicals scheduled for testing, those on test, and those already completed will be published routinely in the **Federal Register** as well as distributed to a variety of newsletters and scientific magazines.

Availability of final reports is announced in the **Federal Register** and released to the news media. Technical reports are sent to regulatory agencies, to members of the peer review committee, to interested members of Congress, to the International Agency for Research on Cancer, to representatives of various countries, and to others requesting copies. Also, condensed versions may be submitted to peer-reviewed scientific journals. Copies are also made available for distribution and sale through the National Technical Information Service.

A mailing list continues to evolve for notices of NTP report availability, for announcements of public meetings, for NTP Technical Bulletins, and for summaries of test results. The NTP has developed a computerized list of about 3,000 people, compiled mainly from those who requested the NTP 1979 Annual Plan, those who attended the August 10th open meeting, and those governmental scientists engaged in toxicology research, management, and related disciplines. The active mailing list will be verified annually. Other agency computer-based name and address collections are available for use by NTP.

An in-depth review is underway to streamline the processes and clearance required for NTP Technical Report preparation and approval.

Interagency Coordination

Other Federal agencies not now participating in the NTP have responsibilities for toxicological research, testing, and communication. The NTP recognizes the need to receive chemical nominations, commentary on the regulatory usefulness of NTP protocols, and active participation from other agencies.

NTP will implement a computer information system in fiscal year 1980 to provide the NTP and others with needed information of the status of chemical testing. The NTP staff will also meet with other national and international agencies to assure understanding of their immediate and long term needs. Clearly, there are a number of other agencies with which coordination will be required.

International Coordination

In partnership with the international community, the NTP will strive to formulate a universally-based communication network of toxicological information. Similarly, the NTP plans to seek the active participation from toxicologists throughout the world. The NTP will explore and develop liaison with foreign agency counterparts. For instance, contacts have been established with the World Health Organization environmental chemicals program, with the International Agency for Research on Cancer, with the International Registry of Potentially Toxic Chemicals, and others. Resultantly, an international peer review group for selected NTP technical reports may be formed.

Public Awareness and Inquiry Response

This project is designed to provide information useful to the general audience, one not trained in toxicology or related disciplines. The NTP will work to understand public questions and concerns and to communicate test results and their significance in an understandable way.

The NTP will transfer knowledge using the written and spoken word. Pamphlets and public communication topics will include basics of toxicological research and testing along with their limitations, current gaps in scientific understanding, the benefit/risk concept, authorities responsible for various toxicological activities, glossary of terms, frequently asked questions and their answers, a list of information officers, and general information about the NTP. To facilitate the overall usability of this service, the NTP will widely publicize an office of information to encourage public inquiries. Moreover, NTP will publish on a regular basis the NTP Technical Bulletin—oriented toward the scientist and the regulator as well as for the administrator and the general audience.

In brief, the NTP Technical Bulletin will contain abstracts of starting and future research activities as well as chemicals nominated and selected for test, protocols, and research results.

Aside from the Annual and Five-Year Plans, the NTP Technical Bulletin will be the main communication medium to keep those persons and groups interested in the NTP informed about the NTP's most current and proposed activities. The Bulletin will also stress a people-places-things theme: who the people are in NTP, what they are doing, what the mission is of each NTP member agency, and profiles about chemicals.

The NTP will survey the readers of the NTP Technical Bulletin for advice about what form and emphasis this communication vehicle should take in the future.

In November 1979, the first issue of the NTP Technical Bulletin was mailed to 2,500 individuals (1,500 on the NTP's mailing list and 1,000 on the Society of Toxicology's members roster).

Annual Report on Carcinogens

(Sec. 262, Pub. L. 95–622, "Biomedical Research and Research Training")

The responsibility to develop these annual reports has been assigned to the NTP. In consultation with the research and regulatory agencies of the NTP Executive Committee, the NTP developed an implementation plan.

The 1979 calendar year report will comprise:

(1) The International Agency for Research on Cancer (IARC) list of 26 human carcinogens as defined in the first 16 IARC Monographs on the Evaluation of Chemicals to Humans.*

(2) The IARC list of 31 animal carcinogens which IARC considers potential human carcinogens.

(3) Those chemicals not included above which are under regulation by the regulatory agencies, and which these agencies consider to be carcinogens.

Subsequent calendar year annual reports will consider other carcinogens as evaluated by IARC as well as other potential chemical carcinogens.

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*Tomatis, L., *et al.* Evaluation of the Carcinogenicity of Chemicals: a review of the Monograph Program of the International Agency for Research on Cancer (1971 to 1977) *Cancer Res., 38*: 877–885, 1978.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

NATIONAL TOXICOLOGY PROGRAM

Review of Current DHEW Research Related to Toxicology [1]

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National Institute of Environmental Health Sciences
Food and Drug Administration
Center for Disease Control/NIOSH and Other

[1] Full Report available upon request.

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